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TITLE OF THE INVENTION

BENZIMIDAZOLES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF USE

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BACKGROUND OF THE INVENTION

The present invention relates to substituted benzimidazole derivatives, compositions containing such compounds and methods of treating type 2 diabetes mellitus.

Diabetes refers to a disease process derived from multiple causative factors and is characterized by elevated levels of plasma glucose (hyperglycemia) in the fasting state or following glucose administration during an oral glucose tolerance test. Frank diabetes mellitus (e.g., a blood glucose level ≥ 126 mg/dL in a fasting state) is associated with increased and premature cardiovascular morbidity and mortality, and is related directly and indirectly to various metabolic conditions, including alterations of lipid, lipoprotein and apolipoprotein metabolism.

Patients with non-insulin dependent diabetes mellitus (type 2 diabetes mellitus), approximately 95% of patients with diabetes mellitus, frequently display elevated levels of serum lipids, such as cholesterol and triglycerides, and have poor blood-lipid profiles, with high levels of LDL-cholesterol and low levels of HDL-cholesterol. Those suffering from Type 2 diabetes mellitus are thus at an increased risk of developing macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension (for example, blood pressure $\geq 130/80$ mmHg in a resting state), nephropathy, neuropathy and retinopathy.

Patients having type 2 diabetes mellitus characteristically exhibit elevated plasma insulin levels compared with nondiabetic patients; these patients have developed a resistance to insulin stimulation of glucose and lipid metabolism in the main insulin-sensitive tissues (muscle, liver and adipose tissues). Thus, Type 2 diabetes, at least early in the natural progression of the disease is characterized primarily by insulin resistance rather than by a decrease in insulin production, resulting in insufficient uptake, oxidation and storage of glucose in muscle, inadequate repression of lipolysis in adipose tissue, and excess glucose production and secretion by the liver. The net effect of decreased sensitivity to insulin is high levels of insulin circulating in the blood without appropriate reduction in plasma glucose (hyperglycemia). Hyperinsulinemia is a risk factor for developing hypertension and may also contribute to vascular disease.

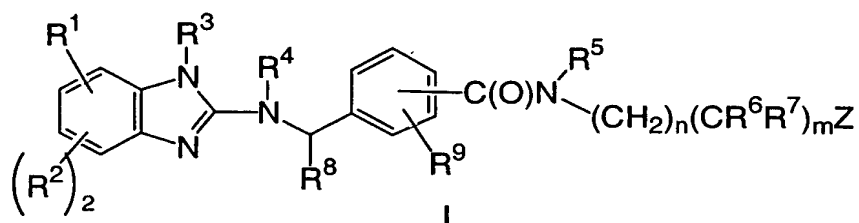
Glucagon serves as the major regulatory hormone attenuating the effect of insulin in its inhibition of liver gluconeogenesis and is normally secreted by pancreatic islet cells in response to falling blood glucose levels. The hormone binds to specific receptors in liver cells that triggers glycogenolysis and an increase in gluconeogenesis through cAMP-mediated events. These responses generate glucose

(e.g. hepatic glucose production) to help maintain euglycemia by preventing blood glucose levels from falling significantly.

In addition to elevated levels of circulating insulin, type II diabetics have elevated levels of plasma glucagon and increased rates of hepatic glucose production. Antagonists of glucagon are useful in improving insulin responsiveness in the liver, decreasing the rate of gluconeogenesis and lowering the rate of hepatic glucose output resulting in a decrease in the levels of plasma glucose.

SUMMARY OF THE INVENTION

The present invention is directed to a compound represented by formula I:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 represents H or is independently selected from the group consisting of:

a) OH, halo, CO_2R^a , $\text{C}(\text{O})\text{NR}^b\text{R}^c$, NR^bR^c , CN or $\text{S}(\text{O})_p\text{R}^d$;

b) $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{OC}_{1-10}\text{alkyl}$, $\text{OC}_{3-10}\text{alkenyl}$ and $\text{OC}_{3-10}\text{alkynyl}$,

said groups being optionally substituted with: (1) 1-5 halo groups up to a perhaloalkyl group; (2) 1 oxo group; (3) 1-2 OH groups; (4) 1-2 $\text{C}_{1-10}\text{alkoxy}$ groups, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO_2R^a group; (5) 1 CO_2R^a or $\text{S}(\text{O})_p\text{R}^d$; (6) 1-2 Aryl, Hetcy or HAR groups, each optionally substituted as follows: (a) 1-5 halo groups, (b) 1 OH, CO_2R^a , CN, $\text{S}(\text{O})_p\text{R}^d$, NO_2 or $\text{C}(\text{O})\text{NR}^b\text{R}^c$ group, (c) 1-2 $\text{C}_{1-10}\text{alkyl}$ or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and (d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo, 1-3 $\text{C}_{1-10}\text{alkyl}$ or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups; (e) $-\text{NR}^a-\text{C}(\text{O})-\text{NR}^b\text{R}^c$; (f) $-\text{NR}^a-\text{CO}_2\text{R}^c$; (g) $-\text{NR}^a-\text{C}(\text{O})\text{R}^c$; (h) $-\text{NR}^b\text{R}^c$; (i) $-\text{NR}^a\text{SO}_2\text{R}^c$; (j) $-\text{SO}_2-\text{NR}^b\text{R}^c$; (k) $-\text{C}(\text{O})\text{NR}^b\text{R}^c$ and (l) $-\text{OC}(\text{O})-\text{NR}^b\text{R}^c$;

c) Aryl, HAR, Hetcy, -O-Aryl, -O-HAR and -O-Hetcy, each optionally substituted as set forth below: (1) 1-3 $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$ or $\text{C}_{2-10}\text{alkynyl}$ groups optionally substituted with 1-5 halo groups; 1-2 OH groups; phenyl optionally substituted with 1-3 halo, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{alkoxy}$ groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups; CO_2R^a ; CN or $\text{S}(\text{O})_p\text{R}^d$ groups; and (2) 1-3 $\text{C}_{1-10}\text{alkoxy}$ groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH; phenyl optionally substituted with 1-3 halo, $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{alkoxy}$ groups, the alkyl

and alkoxy groups being further optionally substituted with 1-3 halo groups; CO_2R^a ; CN or $\text{S}(\text{O})_p\text{R}^d$ groups;

said Aryl, HAR, Hetcy -O-Aryl, -O-HAR and -O-Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of: (3) 1-5 halo groups; (4) 1-2 OH groups; (5) 1 $\text{S}(\text{O})_p\text{R}^d$, NO_2 or CN group; (6) 1-2 CO_2R^a ; (7) $-\text{NR}^a-\text{C}(\text{O})-\text{NR}^b\text{R}^c$; (8) $-\text{NR}^a-\text{CO}_2\text{R}^c$; (9) $-\text{NR}^a-\text{C}(\text{O})\text{R}^c$; (10) $-\text{NR}^b\text{R}^c$; (11) $-\text{NR}^a\text{SO}_2\text{R}^c$; (12) $-\text{SO}_2-\text{NR}^b\text{R}^c$; and (13) $-\text{C}(\text{O})\text{NR}^b\text{R}^c$;

and when R^1 represents Hetcy containing a nitrogen atom, said nitrogen atom can be optionally substituted with a member selected from the group consisting of: (a) $-\text{C}(\text{O})\text{NR}^b\text{R}^c$; (b) $-\text{CO}_2\text{R}^c$; (c) $-\text{C}(\text{O})\text{R}^c$; and (d) $-\text{SO}_2\text{R}^c$;

each R^2 represents H or is independently selected from the group consisting of:

a) OH, halo, CO_2R^a , $\text{C}(\text{O})\text{NR}^b\text{R}^c$, NR^bR^c , CN or $\text{S}(\text{O})_p\text{R}^d$;

b) $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{OC}_{1-10}\text{alkyl}$, $\text{OC}_{3-10}\text{alkenyl}$ and

$\text{OC}_{3-10}\text{alkynyl}$, said groups being optionally substituted with: (1) 1-5 halo groups up to a perhaloalkyl group; (2) 1 oxo group; (3) 1 OH group; (4) 1 $\text{C}_{1-10}\text{alkoxy}$ group, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO_2R^a group; (5) 1 CO_2R^a or $\text{S}(\text{O})_p\text{R}^d$; (6) 1 Aryl, Hetcy or HAR group, each optionally substituted as follows: (a) 1-5 halo groups, (b) 1 OH, CO_2R^a , CN, $\text{S}(\text{O})_p\text{R}^d$, NO_2 or $\text{C}(\text{O})\text{NR}^b\text{R}^c$ group, (c) 1-2 $\text{C}_{1-10}\text{alkyl}$ or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and (d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 $\text{C}_{1-10}\text{alkyl}$ or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo; and 1-2 hydroxy or CO_2R^a groups;

c) Aryl, HAR, Hetcy, -O-Aryl, -O-HAR and -O-Hetcy, each optionally substituted as set forth below: (1) 1-3 $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$ or $\text{C}_{2-10}\text{alkynyl}$ groups optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a , CN or $\text{S}(\text{O})_p\text{R}^d$ groups; (2) 1-3 $\text{C}_{1-10}\text{alkoxy}$ groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a , CN or $\text{S}(\text{O})_p\text{R}^d$ groups;

said Aryl, HAR or Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of: (3) 1-5 halo groups up to perhalo; (4) 1 OH group; (5) 1 $\text{S}(\text{O})_p\text{R}^d$, NO_2 or CN group; and (6) 1 CO_2R^a ;

R^3 represents H or is selected from the group consisting of: a) $\text{C}_{1-10}\text{alkyl}$ or $\text{C}_{2-10}\text{alkenyl}$, each optionally substituted with 1-5 halo groups up to perhalo; 1-2 OH, $\text{C}_{1-3}\text{alkoxy}$ or halo $\text{C}_{1-3}\text{alkoxy}$ groups; 1-2 NR^cR^d groups; and 1-2 Aryl, HAR or Hetcy groups, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2 , $\text{C}_{1-3}\text{alkyl}$, halo $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$ and halo $\text{C}_{1-3}\text{alkoxy}$ groups; and b) Aryl, HAR or Hetcy, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2 , $\text{C}_{1-3}\text{alkyl}$, halo $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$ and halo $\text{C}_{1-3}\text{alkoxy}$ groups;

R^4 is independently selected from the group consisting of:

a) $\text{C}_{1-14}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$ and $\text{C}_{2-10}\text{alkynyl}$, said groups being optionally substituted with: (1) 1-5 halo groups up to perhaloalkyl; (2) 1 oxo group; (3) 1-2 OH groups; (4) 1-2 $\text{C}_{1-10}\text{alkoxy}$

groups, each optionally substituted with up to five halo or a perhaloalkoxy, 1 OH or CO₂R^a group; (5) 1 CO₂R^a or S(O)_pR^d; (6) 1-2 Aryl, Hetcy or HAR groups, each optionally substituted as follows: (i) 1-5 halo groups, (ii) 1 OH, CO₂R^a, CN, S(O)_pR^d, NO₂ or C(O)NR^bR^c group, (iii) 1-2 C₁₋₁₀alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO₂R^a groups; and
 5 (iv) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C₁₋₁₀alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO₂R^a groups;

b) Aryl, HAR or Hetcy, each optionally substituted as follows: (1) 1-3 C₁₋₁₄alkyl, C₂₋₁₀alkenyl or C₂₋₁₀alkynyl groups optionally substituted with 1-5 halo groups, 1-2 OH, CO₂R^a, CN or
 10 S(O)_pR^d groups or phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C₁₋₁₀alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO₂R^a groups; (2) 1-3 C₁₋₁₀alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, CO₂R^a, CN, S(O)_pR^d, and phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C₁₋₁₀alkyl or alkoxy groups, each being further optionally substituted with 1-5
 15 halo up to perhalo, or 1-2 hydroxy or CO₂R^a groups; (3) 1-2 Aryl, HAR or Hetcy, OArlyl, OHAR or OHetcy groups, each optionally substituted as follows: (i) 1-3 halo groups; (ii) 1-2 C₁₋₁₀alkyl, C₂₋₁₀alkenyl or C₂₋₁₀alkynyl groups each optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO₂R^a, CN or S(O)_pR^d groups; (iii) 1-2 C₁₋₁₀alkoxy groups the alkyl portion of which being optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO₂R^a, CN or S(O)_pR^d groups; and (iv) 1-2 CO₂R^a,
 20 S(O)_pR^d, CN, NR^bR^c, NO₂ or OH groups;

said Aryl, HAR or Hetcy group b) being further optionally substituted on carbon by a group selected from the group consisting of: (4) 1-5 halo groups; (5) 1-2 OH groups; (6) 1 S(O)_pR^d, NO₂ or CN group; (7) 1-2 CO₂R^a; (8) -NR^a-C(O)-NR^bR^c; (9) -NR^a-CO₂R^c; (10) -NR^a-C(O)R^c; (11) -NR^bR^c; (12) -NR^aSO₂R^c; (13) -SO₂-NR^bR^c; (14) -C(O)NR^bR^c and -OC(O)-NR^bR^c;

25 and when R⁴ represents Hetcy containing a nitrogen atom, said nitrogen atom can be optionally substituted with a member selected from the group consisting of: (a) -C(O)NR^bR^c; (b) -CO₂R^c; (c) -C(O)R^c; and (d) -SO₂R^c;

R⁵ represents H or C₁₋₆ alkyl;

R⁶ is selected from the group consisting of H, OH, F or C₁₋₃alkyl;

30 R⁷ is H or F, or R⁶ and R⁷ are taken in combination and represent oxo;

R⁸ represents H or C₁₋₆ alkyl, optionally substituted with OH and 1-5 halo groups up to perhalo;

R⁹ represents H, halo, OH, C₁₋₆alkyl, optionally substituted with 1-5 halo groups up to perhalo, or C₁₋₆alkoxy, optionally substituted with 1-3 halo groups up to perhalo,

or when R⁹ is ortho to the benzylic group, R⁸ and R⁹ can be taken together and represent
 35 a -(CH₂)₂₋₄- or a -O-(CH₂)₁₋₃- group;

R^a is H or C_{1-10} alkyl, optionally substituted with phenyl, OH, OC_{1-6} alkyl, CO_2H , CO_2C_{1-6} alkyl and 1-3 halo groups;

R^b is H or C_{1-10} alkyl;

5 R^c is H or is independently selected from: (a) C_{1-10} alkyl, optionally substituted with OH, OC_{1-6} alkyl, CO_2H , CO_2C_{1-6} alkyl, and 1-3 halo groups; (b) Aryl or $Ar-C_{1-6}$ alkyl, each optionally substituted with 1-5 halos and 1-3 members selected from the group consisting of: CN, OH, C_{1-10} alkyl and OC_{1-10} alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; (c) Hetcy or Hetcy- C_{1-6} alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: oxo, C_{1-10} alkyl and OC_{1-10} alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; and (d) HAR or HAR- C_{1-6} alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: C_{1-10} alkyl and OC_{1-10} alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

R^d is C_{1-10} alkyl, Aryl or $Ar-C_{1-10}$ alkyl;

m is an integer selected from 0, 1 and 2;

15 n is an integer selected from 0 to 6;

p is an integer selected from 0, 1 and 2, and

when at least one of m and n is other than 0, Z is selected from CO_2R^a , 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl), and when both m and n are 0, Z is selected from 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl).

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DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

25 "Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl and the like, means carbon chains which may be linear, branched or cyclic, or combinations thereof, containing the indicated number of carbon atoms. If no number is specified, 1-10 carbon atoms are intended for linear or branched alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl and the like. Cycloalkyl is a subset of alkyl; if no number of atoms is specified, 3-10 carbon atoms are intended, forming 1-3 carbocyclic rings that are fused. "Cycloalkyl" also includes monocyclic rings fused to an aryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl and the like.

35 "Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Aryl" (Ar) means mono- and bicyclic aromatic rings containing 6-12 carbon atoms.

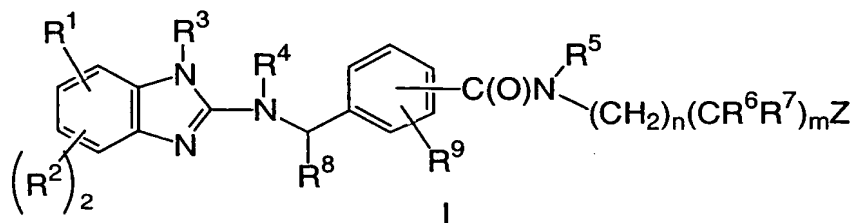
5 Examples of aryl include phenyl, naphthyl, indenyl and the like.

"Heteroaryl" (HAR) means a mono- or bicyclic aromatic ring or ring system containing at least one heteroatom selected from O, S and N, with each ring containing 5 to 6 atoms. Examples include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, 10 benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl and the like. Heteroaryl also includes aromatic heterocyclic groups fused to heterocycles that are non-aromatic or partially aromatic, and aromatic heterocyclic groups fused to cycloalkyl rings. Heteroaryl also includes such groups in charged form, e.g., pyridinium.

"Heterocyclyl" (Hetcy) means mono- and bicyclic saturated rings and ring systems 15 containing at least one heteroatom selected from N, S and O, each of said ring having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen. Examples of "heterocyclyl" include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolyl, tetrahydroisoquinolyl, dihydroindolyl, and the like. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through 20 the nitrogen or N-substituted-(1H,3H)-pyrimidine-2,4-diones (N-substituted uracils). Heterocyclyl moreover includes such moieties in charged form, e.g., piperidinium.

"Halogen" (Halo) includes fluorine, chlorine, bromine and iodine, preferably F and Cl, more preferably F.

In one aspect, the invention is directed to a compound represented by formula I:



25

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R¹ represents H or is independently selected from the group consisting of:

a) OH, halo, CO₂R^a, C(O)NR^bR^c, NR^bR^c, CN or S(O)_pR^d;

b) C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, OC₁₋₁₀alkyl, OC₃₋₁₀alkenyl and OC₃₋₁₀alkynyl,

30 said groups being optionally substituted with: (1) 1-5 halo groups up to a perhaloalkyl group; (2) 1 oxo group; (3) 1-2 OH groups; (4) 1-2 C₁₋₁₀alkoxy groups, each optionally substituted with: up to five halo

or a perhaloalkoxy, 1 OH or CO₂R^a group; (5) 1 CO₂R^a or S(O)_pR^d; (6) 1-2 Aryl, Hetcy or HAR groups, each optionally substituted as follows: (a) 1-5 halo groups, (b) 1 OH, CO₂R^a, CN, S(O)_pR^d, NO₂ or C(O)NR^bR^c group, (c) 1-2 C₁₋₁₀alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO₂R^a groups; and (d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo, 1-3 C₁₋₁₀alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO₂R^a groups; (e) -NR^a-C(O)-NR^bR^c; (f) -NR^a-CO₂R^c; (g) -NR^a-C(O)R^c; (h) -NR^bR^c; (i) -NR^aSO₂R^c; (j) -SO₂-NR^bR^c; (k) -C(O)NR^bR^c and (l) -OC(O)-NR^bR^c;

c) Aryl, HAR, Hetcy, -O-Aryl, -O-HAR and -O-Hetcy, each optionally substituted as set forth below: (1) 1-3 C₁₋₁₀alkyl, C₂₋₁₀alkenyl or C₂₋₁₀alkynyl groups optionally substituted with 1-5 halo groups; 1-2 OH groups; phenyl optionally substituted with 1-3 halo, C₁₋₆ alkyl or C₁₋₆ alkoxy groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups; CO₂R^a; CN or S(O)_pR^d groups; and (2) 1-3 C₁₋₁₀alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH; phenyl optionally substituted with 1-3 halo, C₁₋₆ alkyl or C₁₋₆ alkoxy groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups; CO₂R^a; CN or S(O)_pR^d groups;

said Aryl, HAR, Hetcy -O-Aryl, -O-HAR and -O-Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of: (3) 1-5 halo groups; (4) 1-2 OH groups; (5) 1 S(O)_pR^d, NO₂ or CN group; (6) 1-2 CO₂R^a; (7) -NR^a-C(O)-NR^bR^c; (8) -NR^a-CO₂R^c; (9) -NR^a-C(O)R^c; (10) -NR^bR^c; (11) -NR^aSO₂R^c; (12) -SO₂-NR^bR^c; and (13) -C(O)NR^bR^c; and when R¹ represents Hetcy containing a nitrogen atom, said nitrogen atom can be optionally substituted with a member selected from the group consisting of: (a) -C(O)NR^bR^c; (b) -CO₂R^c; (c) -C(O)R^c; and (d) -SO₂R^c;

each R² represents H or is independently selected from the group consisting of:

a) OH, halo, CO₂R^a, C(O)NR^bR^c, NR^bR^c, CN or S(O)_pR^d;

b) C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, OC₁₋₁₀alkyl, OC₃₋₁₀alkenyl and OC₃₋₁₀alkynyl, said groups being optionally substituted with: (1) 1-5 halo groups up to a perhaloalkyl group; (2) 1 oxo group; (3) 1 OH group; (4) 1 C₁₋₁₀alkoxy group, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO₂R^a group; (5) 1 CO₂R^a or S(O)_pR^d; (6) 1 Aryl, Hetcy or HAR group, each optionally substituted as follows: (a) 1-5 halo groups, (b) 1 OH, CO₂R^a, CN, S(O)_pR^d, NO₂ or C(O)NR^bR^c group, (c) 1-2 C₁₋₁₀alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO₂R^a groups; and (d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C₁₋₁₀alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo; and 1-2 hydroxy or CO₂R^a groups;

c) Aryl, HAR, Hetcy, -O-Aryl, -O-HAR and -O-Hetcy, each optionally substituted as set forth below: (1) 1-3 C₁₋₁₀alkyl, C₂₋₁₀alkenyl or C₂₋₁₀alkynyl groups optionally substituted with 1-5 halo

groups, 1-2 OH, phenyl, CO_2R^a , CN or $\text{S(O)}_p\text{R}^d$ groups; (2) 1-3 C_{1-10} alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a , CN or $\text{S(O)}_p\text{R}^d$ groups;

said Aryl, HAR or Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of; (3) 1-5 halo groups up to perhalo; (4) 1 OH group; (5) 1 $\text{S(O)}_p\text{R}^d$, NO_2 or CN group; (6) 1 CO_2R^a ;

R^3 represents H or is selected from the group consisting of: a) C_{1-10} alkyl or C_{2-10} alkenyl, each optionally substituted with 1-5 halo groups up to perhalo; 1-2 OH, C_{1-3} alkoxy or halo C_{1-3} alkoxy groups; 1-2 NR^cR^d groups; and 1-2 Aryl, HAR or Hetcy groups, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2 , C_{1-3} alkyl, halo C_{1-3} alkyl, C_{1-3} alkoxy and halo C_{1-3} alkoxy groups; and b) Aryl, HAR or Hetcy, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2 , C_{1-3} alkyl, halo C_{1-3} alkyl, C_{1-3} alkoxy and halo C_{1-3} alkoxy groups;

R^4 is independently selected from the group consisting of:

a) C_{1-14} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, said groups being optionally substituted with: (1) 1-5 halo groups up to perhaloalkyl; (2) 1 oxo group; (3) 1-2 OH groups; (4) 1-2 C_{1-10} alkoxy groups, each optionally substituted with up to five halo or a perhaloalkoxy, 1 OH or CO_2R^a group; (5) 1 CO_2R^a or $\text{S(O)}_p\text{R}^d$; (6) 1-2 Aryl, Hetcy or HAR groups, each optionally substituted as follows: (i) 1-5 halo groups, (ii) 1 OH, CO_2R^a , CN, $\text{S(O)}_p\text{R}^d$, NO_2 or $\text{C(O)NR}^b\text{R}^c$ group, (iii) 1-2 C_{1-10} alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and (iv) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10} alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

b) Aryl, HAR or Hetcy, each optionally substituted as follows: (1) 1-3 C_{1-14} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl groups optionally substituted with 1-5 halo groups, 1-2 OH, CO_2R^a , CN or $\text{S(O)}_p\text{R}^d$ groups or phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10} alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups; (2) 1-3 C_{1-10} alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, CO_2R^a , CN, $\text{S(O)}_p\text{R}^d$, and phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10} alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups; (3) 1-2 Aryl, HAR or Hetcy, OAr, OHAR or OHetcy groups, each optionally substituted as follows: (i) 1-3 halo groups; (ii) 1-2 C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl groups each optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a , CN or $\text{S(O)}_p\text{R}^d$ groups; (iii) 1-2 C_{1-10} alkoxy groups the alkyl portion of which being optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a , CN or $\text{S(O)}_p\text{R}^d$ groups; and (iv) 1-2 CO_2R^a , $\text{S(O)}_p\text{R}^d$, CN, NR^bR^c , NO_2 or OH groups;

said Aryl, HAR or Hetcy group b) being further optionally substituted on carbon by a group selected from the group consisting of: (4) 1-5 halo groups; (5) 1-2 OH groups; (6) 1 $\text{S(O)}_p\text{R}^d$, NO_2

or CN group; (7) $1-2 \text{ CO}_2\text{R}^a$; (8) $-\text{NR}^a-\text{C}(\text{O})-\text{NR}^b\text{R}^c$; (9) $-\text{NR}^a-\text{CO}_2\text{R}^c$; (10) $-\text{NR}^a-\text{C}(\text{O})\text{R}^c$; (11) $-\text{NR}^b\text{R}^c$; (12) $-\text{NR}^a\text{SO}_2\text{R}^c$; (13) $-\text{SO}_2-\text{NR}^b\text{R}^c$; (14) $-\text{C}(\text{O})\text{NR}^b\text{R}^c$ and $-\text{OC}(\text{O})-\text{NR}^b\text{R}^c$;

and when R^4 represents Hetcy containing a nitrogen atom, said nitrogen atom can be optionally substituted with a member selected from the group consisting of: (a) $-\text{C}(\text{O})\text{NR}^b\text{R}^c$; (b) -

5 CO_2R^c ; (c) $-\text{C}(\text{O})\text{R}^c$; and (d) $-\text{SO}_2\text{R}^c$;

R^5 represents H or C_{1-6} alkyl;

R^6 is selected from the group consisting of H, OH, F or C_{1-3} alkyl;

R^7 is H or F, or R^6 and R^7 are taken in combination and represent oxo;

R^8 represents H or C_{1-6} alkyl, optionally substituted with OH and 1-5 halo groups up to perhalo;

10 R^9 represents H, halo, OH, C_{1-6} alkyl, optionally substituted with 1-5 halo groups up to perhalo, or C_{1-6} alkoxy, optionally substituted with 1-3 halo groups up to perhalo,

or when R^9 is ortho to the benzylic group, R^8 and R^9 can be taken together and represent a $-(\text{CH}_2)_{2-4}-$ or a $-\text{O}-(\text{CH}_2)_{1-3}-$ group;

15 R^a is H or C_{1-10} alkyl, optionally substituted with phenyl, OH, OC_{1-6} alkyl, CO_2H , $\text{CO}_2\text{C}_{1-6}$ alkyl and 1-3 halo groups;

R^b is H or C_{1-10} alkyl;

20 R^c is H or is independently selected from: (a) C_{1-10} alkyl, optionally substituted with OH, OC_{1-6} alkyl, CO_2H , $\text{CO}_2\text{C}_{1-6}$ alkyl, and 1-3 halo groups; (b) Aryl or $\text{Ar}-\text{C}_{1-6}$ alkyl, each optionally substituted with 1-5 halos and 1-3 members selected from the group consisting of: CN, OH, C_{1-10} alkyl and OC_{1-10} alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; (c) Hetcy or Hetcy- C_{1-6} alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: oxo, C_{1-10} alkyl and OC_{1-10} alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; and (d) HAR or HAR- C_{1-6} alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: C_{1-10} alkyl and OC_{1-10} alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

R^d is C_{1-10} alkyl, Aryl or $\text{Ar}-\text{C}_{1-10}$ alkyl;

m is an integer selected from 0, 1 and 2;

n is an integer selected from 0 to 6;

p is an integer selected from 0, 1 and 2, and

30 when at least one of m and n is other than 0, Z is selected from CO_2R^a , 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl), and when both m and n are 0, Z is selected from 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl).

One aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein R^1 represents H. Within this aspect of the invention, all other variables are as originally defined with respect to formula I.

Another aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein one R^2 represents H, halo or C_{1-6} alkyl, and the other is selected from the group consisting of: H, halo, OH, C_{1-6} alkyl optionally substituted with 1-3 halo groups, C_{1-6} alkoxy optionally substituted with 1-3 halo groups or 1 phenyl or heterocyclic ring, C_{2-4} alkenyl or OC_{2-4} alkenyl. Within this aspect of the invention, all other variables are as originally defined with respect to formula I.

Another aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein R^3 is selected from the group consisting of: H, C_{2-4} alkenyl and C_{1-6} alkyl optionally substituted as follows: a) up to 3 halo groups; b) NR^cR^d wherein R^c and R^d are H or C_{1-4} alkyl; c) OH; and d) Aryl optionally substituted with 1-3 halo groups, C_{1-3} alkyl, OC_{1-3} alkyl, CN, NO_2 , halo C_{1-3} alkyl or O-halo C_{1-3} alkyl. Within this aspect of the invention, all other variables are as originally defined with respect to formula I.

Another aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein R^4 is independently selected from the group consisting of:

- (a) C_{1-14} alkyl, optionally substituted with: (1) 1-5 halo groups up to perhaloalkyl; (2) 1-2 C_{1-10} alkoxy groups, each optionally substituted with 1-5 halo groups up to perhaloalkoxy; (3) 1-2 Aryl groups, each optionally substituted as follows: (i) 1-5 halo groups, (ii) CN or NO_2 , (iii) 1-2 C_{1-10} alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl; and
- (b) Aryl, HAR or Hetcy, each optionally substituted as follows: (1) 1-2 C_{1-10} alkyl or C_{2-10} alkenyl groups, optionally substituted with 1-5 halo groups, phenyl or CO_2R^a groups; (2) 1-2 C_{1-10} alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups; (3) 1-2 Aryl, HAR or Hetcy, OAr, OHAR or OHetcy groups, each optionally substituted as follows: (i) 1-3 halo groups; (ii) 1-2 C_{1-10} alkyl or C_{2-10} alkenyl, each optionally substituted with 1-3 halo groups; (iii) 1-2 C_{1-10} alkoxy groups the alkyl portion of which being optionally substituted with 1-3 halo groups, and (iv) 1-2 CO_2R^a , $S(O)_pR^d$, CN, NR^bR^c , NO_2 or OH groups;

said Aryl, HAR or Hetcy group b) being further optionally substituted on carbon by a group selected from the group consisting of: (4) 1-5 halo groups; (5) 1-2 OH groups; (6) 1 $S(O)_pR^d$, NO_2 or CN group; (7) 1-2 CO_2R^a ; (8) $-NR^a-C(O)-NR^bR^c$; (9) $-NR^a-CO_2R^c$; (10) $-NR^a-C(O)R^c$; (11) $-NR^bR^c$; (12) $-NR^aSO_2R^c$; (13) $-SO_2-NR^bR^c$; (14) $-C(O)NR^bR^c$ and (15) $-OC(O)-NR^bR^c$;

and when R^4 represents Hetcy containing a nitrogen atom, said nitrogen atom can be optionally substituted with a member selected from the group consisting of: (a) $-C(O)NR^bR^c$; (b) $-CO_2R^c$; (c) $-C(O)R^c$; and (d) $-SO_2R^c$. Within this aspect of the invention, all other variables are as originally defined with respect to formula I.

Another aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein R^8 represents H or C_{1-6} alkyl. More

particularly, R^8 represents H or methyl. Within these aspects of the invention, all other variables are as originally defined with respect to formula I.

Another aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein R^9 represents H or halo. Within this aspect of the invention, all other variables are as originally defined with respect to formula I.

Yet another aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein R^8 and R^9 are taken in combination and represent $-(CH_2)_{2-4}-$. More particularly, an aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein R^8 and R^9 are taken in combination and represent ethylene. Within these aspects of the invention, all other variables are as originally defined with respect to formula I.

More particularly, an aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein

R^1 represents H;

one R^2 represents H, halo or C_{1-6} alkyl, and the other is selected from the group consisting of: H, halo, OH, C_{1-6} alkyl optionally substituted with 1-3 halo groups, C_{1-6} alkoxy optionally substituted with 1-3 halo groups or 1 phenyl or heterocyclic ring, C_{2-4} alkenyl or OC_{2-4} alkenyl;

R^3 is selected from the group consisting of: H, C_{2-4} alkenyl and C_{1-6} alkyl optionally substituted as follows: a) up to 3 halo groups; b) NR^cR^d wherein R^c and R^d are H or C_{1-4} alkyl; c) OH; and d) Aryl optionally substituted with 1-3 halo groups, C_{1-3} alkyl, OC_{1-3} alkyl, CN, NO_2 , halo C_{1-3} alkyl or O-halo C_{1-3} alkyl;

R^4 is independently selected from the group consisting of:

(a) C_{1-14} alkyl, optionally substituted with: (1) 1-5 halo groups up to perhaloalkyl; (2) 1-2 C_{1-10} alkoxy groups, each optionally substituted with 1-5 halo groups up to perhaloalkoxy; (3) 1-2 Aryl groups, each optionally substituted as follows: (i) 1-5 halo groups, (ii) CN or NO_2 , (iii) 1-2 C_{1-10} alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl; and

(b) Aryl, HAR or Hetcy, each optionally substituted as follows: (1) 1-2 C_{1-10} alkyl or C_{2-10} alkenyl, optionally substituted with 1-5 halo groups, phenyl or CO_2R^a groups; (2) 1-2 C_{1-10} alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups; (3) 1-2 Aryl, HAR or Hetcy, OArly, OHAR or OHetcy groups, each optionally substituted as follows: (i) 1-3 halo groups; (ii) 1-2 C_{1-10} alkyl or C_{2-10} alkenyl, each optionally substituted with 1-3 halo groups; (iii) 1-2 C_{1-10} alkoxy groups the alkyl portion of which being optionally substituted with 1-3 halo groups, and (iv) 1-2 CO_2R^a , $S(O)_pR^d$, CN, NR^bR^c , NO_2 or OH groups;

said Aryl, HAR or Hetcy group b) being further optionally substituted on carbon by a group selected from the group consisting of: (4) 1-5 halo groups; (5) 1-2 OH groups; (6) 1 $S(O)_pR^d$,

NO₂ or CN group; (7) 1-2 CO₂R^a; (8) -NR^a-C(O)-NR^bR^c; (9) -NR^a-CO₂R^c; (10) -NR^a-C(O)R^c; (11) -NR^bR^c; (12) -NR^aSO₂R^c; (13) -SO₂-NR^bR^c; (14) -C(O)NR^bR^c and (15) -OC(O)-NR^bR^c;

and when R⁴ represents Hetcy containing a nitrogen atom, said nitrogen atom can be optionally substituted with a member selected from the group consisting of: (a) -C(O)NR^bR^c; (b) -CO₂R^c; (c) -C(O)R^c; and (d) -SO₂R^c;

R⁸ represents H or C₁₋₆ alkyl;

R⁹ represents H or halo;

R⁵ represents H or C₁₋₆ alkyl;

R⁶ is selected from the group consisting of H, OH, F or C₁₋₃alkyl;

R⁷ is H or F, or R⁶ and R⁷ are taken in combination and represent oxo;

R^a is H or C₁₋₁₀alkyl, optionally substituted with phenyl, OH, OC₁₋₆alkyl, CO₂H, CO₂C₁₋₆alkyl and 1-3 halo groups;

R^b is H or C₁₋₁₀alkyl;

R^c is H or is independently selected from: (a) C₁₋₁₀alkyl, optionally substituted with OH, OC₁₋₆alkyl, CO₂H, CO₂C₁₋₆alkyl, and 1-3 halo groups; (b) Aryl or Ar-C₁₋₆alkyl, each optionally substituted with 1-5 halos and 1-3 members selected from the group consisting of: CN, OH, C₁₋₁₀alkyl and OC₁₋₁₀alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; (c) Hetcy or Hetcy-C₁₋₆alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: oxo, C₁₋₁₀alkyl and OC₁₋₁₀alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; and (d) HAR or HAR-C₁₋₆alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: C₁₋₁₀alkyl and OC₁₋₁₀alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

R^d is C₁₋₁₀alkyl, Aryl or Ar-C₁₋₁₀alkyl;

m is an integer selected from 0, 1 and 2;

n is an integer selected from 0 to 6;

p is an integer selected from 0, 1 and 2, and

when at least one of m and n is other than 0, Z is selected from CO₂R^a, 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl), and when both m and n are 0, Z is selected from 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl). Within this aspect of the invention, all other variables are as originally defined with respect to formula I.

Another more particular aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof wherein:

R¹ represents H;

one R² represents H, halo or C₁₋₆alkyl, and the other is selected from the group consisting of: H, halo, OH, C₁₋₆alkyl optionally substituted with 1-3 halo groups, C₁₋₆alkoxy optionally substituted with 1-3 halo groups or 1 phenyl or heterocyclic ring, C₂₋₄alkenyl or OC₂₋₄alkenyl;

R^3 is selected from the group consisting of: H, C_{2-4} alkenyl and C_{1-6} alkyl optionally substituted as follows: a) up to 3 halo groups; b) NR^cR^d wherein R^c and R^d are H or C_{1-4} alkyl; c) OH; and d) Aryl optionally substituted with 1-3 halo groups, C_{1-3} alkyl, OC_{1-3} alkyl, CN, NO_2 , halo C_{1-3} alkyl or O-halo C_{1-3} alkyl;

5 R^4 is independently selected from the group consisting of:

a) C_{1-14} alkyl, optionally substituted with: (1) 1-5 halo groups up to perhaloalkyl; (2) 1-2 C_{1-10} alkoxy groups, each optionally substituted with 1-5 halo groups up to perhaloalkoxy; (3) 1-2 Aryl groups, each optionally substituted as follows: (i) 1-5 halo groups, (ii) CN or NO_2 , and (iii) 1-2 C_{1-10} alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl; and

10 b) Aryl, HAR or Hetcy, each optionally substituted as follows: (1) 1-2 C_{1-10} alkyl or C_{2-10} alkenyl, optionally substituted with 1-5 halo groups, phenyl or CO_2R^a groups; (2) 1-2 C_{1-10} alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups; (3) 1-2 Aryl, HAR or Hetcy, OAr, OHAR or OHetcy groups, each optionally substituted as follows: (a) 1-3 halo groups; (b) 1-2 C_{1-10} alkyl or C_{2-10} alkenyl, each optionally substituted with 1-3 halo groups; (c) 1-2 C_{1-10} alkoxy groups the alkyl portion of which being optionally substituted with 1-3 halo groups, and (d) 1-2 CO_2R^a , $S(O)_pR^d$, CN, NR^bR^c , NO_2 or OH groups;

said Aryl, HAR or Hetcy group b) being further optionally substituted on carbon by a group selected from the group consisting of: (4) 1-5 halo groups; (5) 1-2 OH groups; (6) 1 $S(O)_pR^d$, NO_2 or CN group; (7) 1-2 CO_2R^a ; (8) $-NR^a-C(O)-NR^bR^c$; (9) $-NR^a-CO_2R^c$; (10) $-NR^a-C(O)R^c$; (11) $-NR^bR^c$; (12) $-NR^aSO_2R^c$; (13) $-SO_2-NR^bR^c$; (14) $-C(O)NR^bR^c$ and (15) $-OC(O)-NR^bR^c$;

20 and when R^4 represents Hetcy containing a nitrogen atom, said nitrogen atom can be optionally substituted with a member selected from the group consisting of: (a) $-C(O)NR^bR^c$; (b) $-CO_2R^c$; (c) $-C(O)R^c$; and (d) $-SO_2R^c$;

R^8 and R^9 are taken in combination and represent $-(CH_2)_{2-4}-$;

25 R^5 represents H or C_{1-6} alkyl;

R^6 is selected from the group consisting of H, OH, F or C_{1-3} alkyl;

R^7 is H or F, or R^6 and R^7 are taken in combination and represent oxo;

R^a is H or C_{1-10} alkyl, optionally substituted with phenyl, OH, OC_{1-6} alkyl, CO_2H , CO_2C_{1-6} alkyl and 1-3 halo groups;

30 R^b is H or C_{1-10} alkyl;

R^c is H or is independently selected from: (a) C_{1-10} alkyl, optionally substituted with OH, OC_{1-6} alkyl, CO_2H , CO_2C_{1-6} alkyl, and 1-3 halo groups; (b) Aryl or Ar- C_{1-6} alkyl, each optionally substituted with 1-5 halos and 1-3 members selected from the group consisting of: CN, OH, C_{1-10} alkyl and OC_{1-10} alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; (c) Hetcy or Hetcy- C_{1-6} alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: oxo, C_{1-10} alkyl and OC_{1-10} alkyl, said alkyl and alkoxy being further optionally substituted

with 1-5 halo groups up to perhalo; and (d) HAR or HAR-C₁₋₆alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: C₁₋₁₀alkyl and OC₁₋₁₀alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

R^d is C₁₋₁₀alkyl, Aryl or Ar-C₁₋₁₀alkyl;

m is an integer selected from 0, 1 and 2;

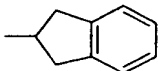
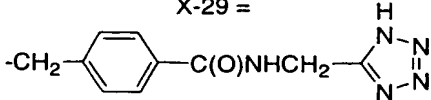
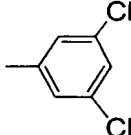
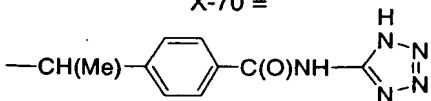
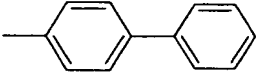
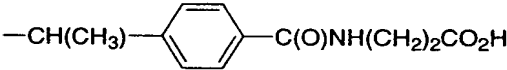
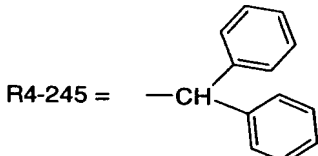
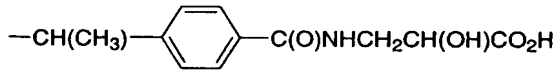

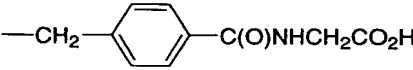
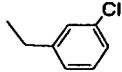
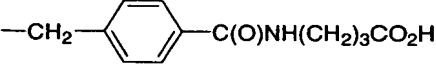
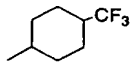
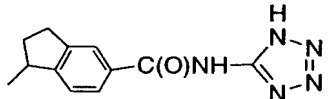
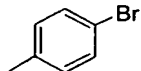
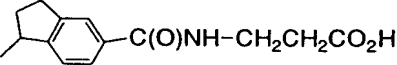
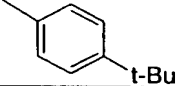
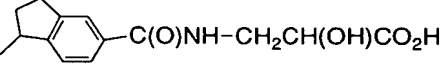
n is an integer selected from 0 to 6;

p is an integer selected from 0, 1 and 2, and

when at least one of m and n is other than 0, Z is selected from CO₂R^a, 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl), and when both m and n are 0, Z is selected from 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl). Within this aspect of the invention, all other variables are as originally defined with respect to formula I

Selected compounds of the invention that are of interest are shown in the table below.

<p style="text-align: center;">TABLE A</p> <p style="text-align: center;">Key to Compounds</p> <div style="text-align: center;"> </div> <p>wherein R², R³ and R⁴ are in accordance with formula I and X is as shown below.</p> <div style="text-align: center;"> </div>	
<p>R4-1 =</p>	<p>X-1 =</p>
<p>R4-2 =</p>	<p>X-3 =</p>
<p>R4-54 =</p>	<p>X-19 =</p>
<p>R4-95 =</p>	<p>X-21 =</p>

<p>R4-113 =</p> 	<p>X-29 =</p> 
<p>R4-122 =</p> 	<p>X-70 =</p> 
<p>R4-238 =</p> 	<p>X-85 =</p> 
<p>R4-245 =</p> 	<p>X-86 =</p> 
<p>R4-256 =</p> 	<p>X-226 =</p> 
<p>R4-258 =</p> 	<p>X-227 =</p> 
<p>R4-260 =</p> 	<p>X-237 =</p> 
<p>R4-261 =</p> 	<p>X-238 =</p> 
<p>R4-262 =</p> 	<p>X-239 =</p> 

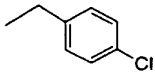
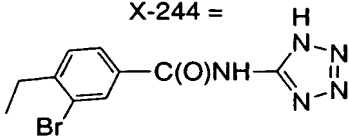
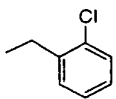
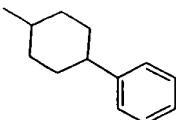
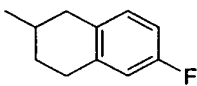
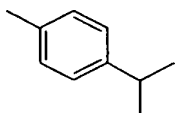
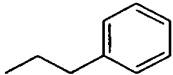
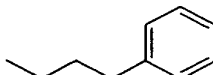
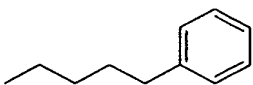
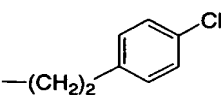
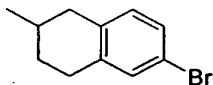
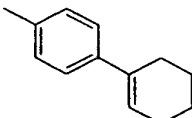
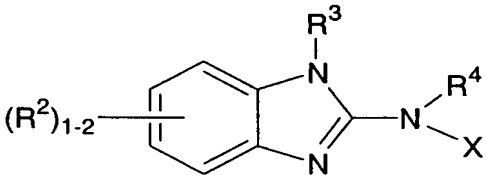
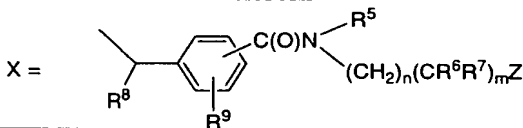



R4-265 = 	X-244 = 
R4-266 = 	R4-267 = 
R4-269 = 	R4-273 = 
R4-275 = 	R4-276 = 
R4-277 = 	R4-278 = 
R4-282 = 	R4-284 = 

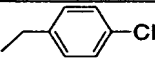
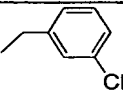
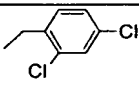
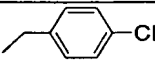
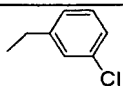
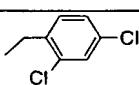
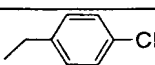
TABLE A				
 <p>wherein</p> <p>X = </p>				
Cpd No.	R ²	R ³	R ⁴	X
1	5-Me	H	R4-1	X-1
2	5-Me	H	R4-2	X-1
3	5-Me	H	R4-1	X-3

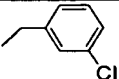
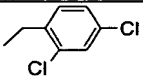
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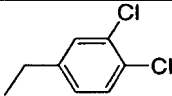
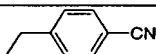
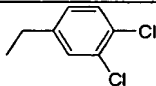

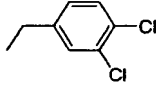


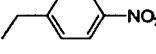
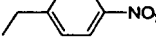
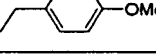
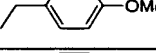
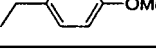
4	5-Me	H	R4-2	X-3
5	5-OCF ₃	H	R4-1	X-1
6	5-OCF ₃	H	R4-2	X-3
7	5-OCF ₃	H	R4-2	X-1
8	6-Me	Me	R4-2	X-3
9	5-Cl	H	R4-2	X-3
10	5-Cl	H	R4-1	X-3
11	6-Me	Me	R4-2	X-1
12	5-Cl	H	R4-2	X-1
13	5-Cl	H	R4-1	X-1
14	5-Me	Me	R4-1	X-3
15	5-Me	Me	R4-1	X-1
16	H	H	R4-2	X-3
17	H	H	R4-2	X-1
18	H	Me	R4-2	X-1
19	H	Me	R4-2	X-19
20	H	Me	R4-2	X-3
21	H	Me	R4-2	X-21
22	6-Me	Me	R4-2	X-21
23	5-Me	H	R4-2	X-21
24	H	Et	R4-2	X-3
25	H	Et	R4-2	X-1
26	H	Et	R4-2	X-21
27	H	n-Pr	R4-2	X-3
28	H	n-Pr	R4-2	X-1
29	H	n-Pr	R4-2	X-29
30	H	n-Pr	R4-2	X-21
31	5-Me	H	R4-2	X-29
32	H	cPentyl	R4-2	X-3
33	H	cPentyl	R4-2	X-1
34	H	cPentyl	R4-2	X-21
35	H	Et	R4-2	X-29
36	H	Benzyl	R4-2	X-3
37	H	Benzyl	R4-2	X-29
38	H	Benzyl	R4-2	X-1

39	H	Benzyl	R4-2	X-21
40	H	-CH ₂ CH(Me) ₂	R4-2	X-3
41	H	-CH ₂ CH(Me) ₂	R4-2	X-29
42	H	-CH ₂ CH(Me) ₂	R4-2	X-1
43	H	-CH ₂ CH(Me) ₂	R4-2	X-21
44	H	H	R4-2	X-29
45	H	H	R4-2	X-21
46	H	Me	R4-2	X-29
47	H	CH ₂ CH ₂ F	R4-2	X-3
48	H	CH ₂ CH ₂ F	R4-2	X-1
49	H	CH ₂ CH ₂ F	R4-2	X-21
50	H	CH ₂ CH ₂ F	R4-2	X-29
51	H	CH ₂ CH=CH ₂	R4-2	X-3
52	H	CH ₂ CH=CH ₂	R4-2	X-1
53	H	CH ₂ CH=CH ₂	R4-2	X-21
54	H	H	R4-54	X-3
55	H	H	R4-54	X-1
56	H	H	R4-54	X-21
57	H	Me	R4-54	X-3
58	H	Me	R4-54	X-1
59	H	Me	R4-54	X-21
60	5,6-di-Cl	H	R4-2	X-3
61	5,6-di-Cl	H	R4-2	X-29
62	5,6-di-Cl	H	R4-2	X-1
63	5,6-di-Cl	H	R4-2	X-21
64	5,6-di-Cl	Et	R4-2	X-3
65	5,6-di-Me	H	R4-2	X-3
66	5,6-di-Me	H	R4-2	X-29
67	5,6-di-Me	H	R4-2	X-1
68	5,6-di-Me	H	R4-2	X-21
69	H	Me	R4-2	X-70
70	H	CH ₂ CH ₂ OH	R4-2	X-3
71	H	CH ₂ CH ₂ OH	R4-2	X-1
72	H	CH ₂ CH ₂ OH	R4-2	X-21
73	5,6-di-Me	Me	R4-2	X-3


74	5,6-di-Me	Me	R4-2	X-29
75	5,6-di-Me	Me	R4-2	X-1
76	5,6-di-Me	Me	R4-2	X-21
77	5,6-di-Cl	Me	R4-2	X-3
78	5,6-di-Cl	Me	R4-2	X-1
79	5,6-di-Cl	Me	R4-2	X-21
80	5,6-di-F	H	R4-2	x-3
81	5,6-di-F	H	R4-2	x-1
82	5,6-di-F	H	R4-2	x-29
83	5,6-di-F	H	R4-2	x-21
84	H	Me	R4-2	x-85
85	H	Me	R4-2	X-86
86	5,6-di-F	Me	R4-2	X-3
87	5,6-di-F	Me	R4-2	X-1
88	5,6-di-F	Me	R4-2	X-21
89	H	(CH ₂) ₃ OH	R4-2	X-3
90	H	(CH ₂) ₃ OH	R4-2	X-21
91	H	Me	R4-95	X-3
92	H	Me	R4-95	X-21
93	H	(CH ₂) ₂ NMe ₂	R4-2	X-3
94	H		R4-2	X-3
95	H		R4-2	X-21
96	H		R4-2	X-1
97	H	Phenyl	R4-2	X-3
98	H	Phenyl	R4-2	X-29
99	H	Phenyl	R4-2	X-1
100	H	Phenyl	R4-2	X-21
101	6-allyloxy	Et	R4-2	X-3
102	6-allyloxy	Et	R4-2	X-1
103	6-allyloxy	Et	R4-2	X-21
104	6-allyloxy	Et	R4-2	X-29
105	5,6-di-F	Et	R4-2	X-3
106	H	Me	R4-113	X-3
107	5,6-di-F	Et	R4-2	X-21
108	6-OH	Et	R4-2	X-3

109	6-OH	Et	R4-2	X-1
110	5,6-di-F	Et	R4-2	X-1
111	6-OH	Et	R4-2	X-21
112	6-OH	Et	R4-2	X-29
113	5-OMe	Me	R4-2	X-3
114	5-OMe	Me	R4-2	X-21
115	5-OMe	Me	R4-2	X-1
116	H	H	R4-122	X-3
117	H	H	R4-122	X-1
118	H	H	R4-122	X-21
119	H	H	R4-122	X-29
120	5-OH	Me	R4-2	X-3
121	5-OH	Me	R4-2	X-1
122	5-OH	Me	R4-2	X-21
123	5-allyloxy	Me	R4-2	X-3
124	5-allyloxy	Me	R4-2	X-1
125	5-benzyloxy	Me	R4-2	X-3
126	5-benzyloxy	Me	R4-2	X-1
127	6-allyloxy	Me	R4-2	X-3
128	6-allyloxy	Me	R4-2	X-1
129	6-allyloxy	Me	R4-2	X-21
130	6-allyloxy	Me	R4-2	X-29
131	H		R4-2	X-3
132	H		R4-2	X-3
133	H		R4-2	X-3
134	H		R4-2	X-21
135	H		R4-2	X-21
136	H		R4-2	X-21
137	H		R4-2	X-1

138	H		R4-2	X-1
139	H		R4-2	X-1
140	6-OH	Me	R4-2	X-3
141	6-OH	Me	R4-2	X-1
142	6-OH	Me	R4-2	X-21
143	6-OH	Me	R4-2	X-29
144	5-n-propyloxy	Me	R4-2	X-3
145	5-n-propyloxy	Me	R4-2	X-29
146	5-n-propyloxy	Me	R4-2	X-1
147	5-n-propyloxy	Me	R4-2	X-21
148	5-isopropyl oxy	Me	R4-2	X-3
149	5-isopropyl oxy	Me	R4-2	X-29
150	5-isopropyl oxy	Me	R4-2	X-1
151	5-isopropyl oxy	Me	R4-2	X-21
152	6-n-propyloxy	Me	R4-2	X-3
153	6-n-propyloxy	Me	R4-2	X-1
154	6-n-propyloxy	Me	R4-2	X-21
155	5-OMe	Me	R4-2	X-29
156	5-cyclo-pentyloxy	Me	R4-2	X-3
157	5-cyclo-pentyloxy	Me	R4-2	X-29
158	5-OCH ₂ CH(Me) ₂	Me	R4-2	X-3
159	5-OCH ₂ CH(Me) ₂	Me	R4-2	X-29
160	6-benzyloxy	Me	R4-2	X-3
161	6-isopropyloxy	Me	R4-2	X-3
162	6-OMe	Me	R4-2	X-3
163	6-benzyloxy	Me	R4-2	X-1
164	6-isopropyloxy	Me	R4-2	X-1
165	6-OMe	Me	R4-2	X-1
166	6-benzyloxy	Me	R4-2	X-21
167	6-isopropyloxy	Me	R4-2	X-21
168	6-OMe	Me	R4-2	X-21
169	5-benzyloxy	Me	R4-2	X-21

170	5-cyclopentyloxy	Me	R4-2	X-1
171	5-cyclopentyloxy	Me	R4-2	X-21
172	5-isobutyloxy	Me	R4-2	X-1
173	5-isobutyloxy	Me	R4-2	X-21
174	6-allyloxy	Me	R4-113	X-3
175	6-allyloxy	Me	R4-113	X-1
176	H		R4-2	X-3
177	6-allyloxy	Me	R4-113	X-21
178	H		R4-2	X-3
179	H		R4-2	X-21
180	H		R4-2	X-21
181	H		R4-2	X-1
182	H		R4-2	X-1
183	H		R4-2	X-3
184	H		R4-2	X-21
185	H		R4-2	X-1
186	H		R4-2	X-3
187	H		R4-2	X-21
188	H		R4-2	X-1
189	H	Me	R4-2	X-237
190	H	Me	R4-2	X-238
191	H	Me	R4-2	X-239
192	6-cyclopentyloxy	Me	R4-2	X-3
193	6-cyclopentyloxy	Me	R4-2	X-1
194	6-cyclopentyloxy	Me	R4-2	X-21
195	5-OMe	Me	R4-54	X-3
196	5-OMe	Me	R4-54	X-1

197	6-allyloxy	Me	R4-95	X-3
198	6-allyloxy	Me	R4-95	X-1
199	6-allyloxy	Me	R4-95	X-21
200	6-OH	Me	R4-95	X-3
201	5-OEt	Me	R4-2	X-3
202	5-cyclobutyloxy	Me	R4-2	X-3
203	5-cyclopropyl methoxy	Me	R4-2	X-3
204	5-cyclopropyl methoxy	Me	R4-2	X-1
205	5-cyclohexyl methoxy	Me	R4-2	X-3
206	5-cyclohexyl methoxy	Me	R4-2	X-1
207	5-OEt	Me	R4-2	X-1
208	5-cyclobutyloxy	Me	R4-2	X-1
209	5-OCH ₂ CHF ₂	Me	R4-2	X-3
210	5-OCH ₂ CHF ₂	Me	R4-2	X-1
211	5-cyclobutyl methoxy	Me	R4-2	X-3
212	5-cyclobutyl methoxy	Me	R4-2	X-1
213	5-cyclopentyl methoxy	Me	R4-2	X-3
214	5-cyclopentyl methoxy	Me	R4-2	X-1
215	6-n-propyloxy	Me	R4-95	X-3
216	5-CF ₃	Me	R4-2	X-3
217	6-benzyloxy	Me	R4-95	X-3
218	5-CF ₃	Me	R4-2	X-1
219	5-n-propyloxy	Me	R4-54	X-3
220	6-n-propyloxy	Me	R4-95	X-1
221	6-benzyloxy	Me	R4-95	X-1
222	6-OEt	Me	R4-2	X-3
223	6-cyclopropyl methoxy	Me	R4-2	X-3
224	6-OCH ₂ CH(Me) ₂	Me	R4-2	X-3
225	6-OEt	Me	R4-2	X-1
226	6-cyclopropyl methoxy	Me	R4-2	X-1
227	6-OCH ₂ CH(Me) ₂	Me	R4-2	X-1

228	H	Me	R4-54	X-237
229	5-Br	Me	R4-2	X-3
230	5-Br	Me	R4-2	X-1
231	H	Et	R4-2	X-226
232	H	Et	R4-2	X-227
233	6-OCH ₂ CHF ₂	Me	R4-2	X-3
234	6-OCH ₂ CHF ₂	Me	R4-2	X-1
235	5-OMe	Me	R4-2	X-244
236	H	Me	R4-245	X-3
237	6-cyclohexyloxy	Me	R4-2	X-3
238	H	Me	R4-122	X-3
249	5-n-propyloxy	Me	R4-2	X-237
240	5-cyclopentyloxy	Me	R4-54	X-3
241	5-cyclopentyloxy	Me	R4-54	X-1
242	5-n-propyloxy	Me	R4-54	X-1
243	6-cyclohexyl methoxy	Me	R4-2	X-3
244	6-cyclohexyloxy	Me	R4-2	X-1
245	6-cyclohexyl methoxy	Me	R4-2	X-1
246	H	Me	R4-256	X-1
247	6- -OCH ₂ CH ₂ -N 	Me	R4-2	X-3
248	5-OMe	Me	R4-258	X-3
249	5-cyclopentyloxy	Me	R4-2	X-244
250	H	Me	R4-260	X-3
251	H	Me	R4-261	X-3
252	H	Me	R4-262	X-3
253	H	Me	R4-262	X-1
254	5-OMe	Me	R4-122	X-3
255	5-OMe	Me	R4-265	X-3
256	5-OMe	Me	R4-266	X-3
257	H	Me	R4-267	X-1
258	H	Me	R4-267	X-3
259	H	Me	R4-269	X-1
260	H	Me	R4-269	X-3

261	H	Me	R4-238	X-3
262	H	Me	R4-238	X-1
263	H	Me	R4-273	X-3
264	H	Me	R4-273	X-1
265	H	Me	R4-275	X-3
266	H	Me	R4-276	X-3
267	H	Me	R4-277	X-3
268	H	Me	R4-278	X-3
269	H	Me	R4-278	X-1
270	5-n-pentyloxy	Me	R4-122	X-3
271	5-n-propyloxy	Me	R4-122	X-3
272	H	Me	R4-282	X-1
273	H	Me	R4-282	X-3
274	H	Me	R4-284	X-3
275	H	Me	R4-284	X-1
276	5-OCF ₃	Me	R4-95	X-3
277	5-CF ₃	Me	R4-95	X-3
278	5-Cl	Me	R4-95	X-3
279	5-OMe	Me	R4-95	X-3
278	5-OMe	Me	R4-95	X-1
281	5-n-propyloxy	Me	R4-95	X-3
282	5-cyclopentyloxy	Me	R4-95	X-3

as well as the pharmaceutically acceptable salts and solvates thereof.

The invention further includes a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

5 Also included is a method of treating type 2 diabetes mellitus in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount that is effective to treat type 2 diabetes mellitus.

Also included is a method of preventing or delaying the onset of type 2 diabetes mellitus in a mammalian patient in need thereof, comprising administering to said patient a compound of formula I in an amount that is effective to prevent or delay the onset of type 2 diabetes mellitus.

10 Also included is a method of treating hyperglycemia, diabetes or insulin resistance in a mammalian patient in need of such treatment which comprises administering to said patient an effective amount of a compound of formula I.

Also included is a method of treating, preventing or delaying the onset of diseases or conditions that are associated with type 2 diabetes mellitus. Examples include diseases and conditions selected from the group consisting of: dyslipidemias, (e.g., hyperlipidemia), such as elevated levels of cholesterol (hypercholesterolemia), triglycerides (hypertriglyceridemia) or low density lipoproteins (LDL) (high LDL levels), low levels of high density lipoprotein (HDL), microvascular or macrovascular changes and the sequelae of such conditions, such as coronary heart disease, stroke, peripheral vascular disease, hypertension, renal hypertension, nephropathy, neuropathy and retinopathy. The method entails administering to a type 2 diabetic patient, e.g., a human patient, an amount of a compound of formula I that is effective for treating, preventing or delaying the onset of such diseases or conditions.

Also included is a method of treating atherosclerosis in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount effective to treat atherosclerosis.

Also included is a method of treating a condition selected from the group consisting of: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, and other conditions and disorders where insulin resistance is a component, in a mammalian patient in need of such treatment, comprising administering to the patient a compound in accordance with formula I in an amount that is effective to treat said condition.

Also included is a method of delaying the onset of a condition selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, and other conditions and disorders where insulin resistance is a component in a mammalian patient in need thereof, comprising administering to the patient a compound of formula I in an amount that is effective to delay the onset of said condition.

Also included is a method of reducing the risk of developing a condition selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, and other conditions and disorders where insulin resistance is a component in a mammalian patient in need of such treatment,

comprising administering to the patient a compound of formula I in an amount that is effective to reduce the risk of developing said condition.

Optical Isomers - Diastereomers - Geometric Isomers – Tautomers

5 Many of the compounds of formula I contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention includes all such isomeric forms of the compounds, in pure form as well as in mixtures.

10 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

15

Salts and Solvates

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable substantially non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids, as well as salts that can be converted into pharmaceutically acceptable salts. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

25

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

35

Solvates as used herein refers to the compound of formula I or a salt thereof, in association with a solvent, such as water. Representative examples include hydrates, hemihydrates, trihydrates and the like.

5 References to the compounds of Formula I include the pharmaceutically acceptable salts and solvates.

This invention relates to method of antagonizing or inhibiting the production or activity of glucagon, thereby reducing the rate of gluconeogenesis and glycogenolysis, and the concentration of glucose in plasma.

10 The compounds of formula I can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of disease states in mammals caused by elevated levels of glucose, comprised of combining the compound of formula I with the carrier materials to provide the medicament.

Dose Ranges

15 The prophylactic or therapeutic dose of the compound of formula I will, of course, vary with the nature of the condition to be treated, the particular compound selected and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight, preferably about 0.01 mg to about 50 mg per kg, and more preferably 0.1 to 10 mg per kg, in single or divided doses. It may be necessary to use dosages outside of these limits in some cases. The
20 terms "effective amount" "anti-diabetic effective amount" and the other terms appearing throughout the application addressing the amount of the compound to be used refer to the dosage ranges provided, taking into account any necessary variation outside of these ranges, as determined by the skilled physician.

Representative dosages for adults range from about 0.1 mg to about 1.0 g per day, preferably about 1 mg to about 200 mg, in single or divided doses.

25 When intravenous or oral administration is employed, a representative dosage range is from about 0.001 mg to about 100 mg (preferably from 0.01 mg to about 10 mg) of a compound of Formula I per kg of body weight per day, and more preferably, about 0.1 mg to about 10 mg of a compound of Formula I per kg of body weight per day.

30 Pharmaceutical Compositions

As mentioned above, the pharmaceutical composition comprises a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier. The term "composition" encompasses a product comprising the active and inert ingredient(s), (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results,
35 directly or indirectly, from the combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or

interactions between ingredients. Preferably the composition is comprised of a compound of formula I in an amount that is effective to treat, prevent or delay the onset of type 2 diabetes mellitus, in combination with the pharmaceutically acceptable carrier.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Examples of dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols and the like, with oral tablets being preferred. Thus, one aspect of the invention that is of interest is the use of a compound of formula I for preparing a pharmaceutical composition which is comprised of combining the compound of formula I with the carrier.

In preparing oral compositions, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquids, e.g., suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solids, e.g., powders, capsules and tablets, with the solid oral preparations being preferred. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 1g of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

The following are examples of pharmaceutical dosage forms for the compounds of

Formula I:

Injectable Suspension (I.M.)	mg/mL	Tablet	mg/tablet
Compound of Formula I	10.0	Compound of Formula I	25
Methylcellulose	5.0	Microcrystalline Cellulose	415
Tween 80	0.5	Povidone	14.0
Benzyl alcohol	9.0	Pregelatinized Starch	43.5
Benzalkonium chloride	1.0	Magnesium Stearate	2.5
Water for injection to make	1.0 mL	Total	500mg
Capsule	mg/capsule	Aerosol	Per canister
Compound of Formula I	25.0	Compound of Formula I	24 mg
Lactose Powder	573.5	Lecithin, NF Liq. Conc.	1.2 mg
Magnesium Stearate	1.5	Trichlorofluoromethane, NF	4.025 g
Total	600mg	Dichlorodifluoromethane, NF	12.15 g

Combination Therapy

- 5 Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/delaying the onset of type 2 diabetes mellitus, as well as the diseases and conditions associated with type 2 diabetes mellitus, for which compounds of Formula I are useful. Other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used with one or more
- 10 other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a)
- 15 bis-guanides (e.g., buformin, metformin, phenformin), (b) PPAR agonists (e.g., troglitazone, pioglitazone, rosiglitazone), (c) insulin, (d) somatostatin, (e) α -glucosidase inhibitors (e.g., voglibose, miglitol, acarbose), (f) DP-IV inhibitors, (g) LXR modulators and (h) insulin secretagogues (e.g., acetohexamide, carbutamide, chlorpropamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidine, glixoepid, glyburide, glyhexamide, glypinamide, phenbutamide, tolazamide, tolbutamide, tolcyclamide,
- 20 nateglinide and repaglinide).

The weight ratio of the compound of the Formula I to the second active ingredient may be varied within wide limits and depends upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined

with a PPAR agonist the weight ratio of the compound of the Formula I to the PPAR agonist will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200.

Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

5 For combination products, the compound of formula I may be combined with any other active ingredients and then added to the carrier ingredients; alternatively the order of mixing may be varied.

Examples of pharmaceutical combination compositions include: 1) a compound according to formula I, 2) a compound selected from the group consisting of: a) DP-IV inhibitors; b) 10 insulin sensitizers selected from the group consisting of (i) PPAR agonists and (ii) biguanides; c) insulin and insulin mimetics; d) sulfonylureas and other insulin secretagogues; e) alpha glucosidase inhibitors; f) glucagon receptor antagonists; g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; h) GIP, GIP mimetics, and GIP receptor agonists; i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists; j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, 15 (ii) sequestrants, (iii) nicotiny alcohol, nicotinic acid or a salt thereof, (iv) PPAR alpha agonists, (v) PPAR alpha/gamma dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, (viii) anti-oxidants and (ix) LXR modulators; (k) PPAR delta agonists; (l) antiobesity compounds; (m) an ileal bile acid transporter inhibitor; (n) anti-inflammatory agents other than glucocorticoids; and (o) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; and 3) a 20 pharmaceutically acceptable carrier.

A method that is of particular interest relates to a method of treating, preventing or delaying the onset of diabetes, and in particular, type 2 diabetes, in a mammalian patient in need thereof, comprising administering to the patient 1) a compound according to formula I, and 2) a compound selected from the group consisting of: a) DP-IV inhibitors; b) insulin sensitizers selected from the 25 group consisting of (i) PPAR agonists and (ii) biguanides; c) insulin and insulin mimetics; d) sulfonylureas and other insulin secretagogues; e) alpha glucosidase inhibitors; f) glucagon receptor antagonists; g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; h) GIP, GIP mimetics, and GIP receptor agonists; i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists; j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, (ii) 30 sequestrants, (iii) nicotiny alcohol, nicotinic acid or a salt thereof, (iv) PPAR alpha agonists, (v) PPAR alpha/gamma dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, (viii) anti-oxidants and (ix) LXR modulators; (k) PPAR delta agonists; (l) antiobesity compounds; (m) an ileal bile acid transporter inhibitor; (n) anti-inflammatory agents other than glucocorticoids; and (o) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; said compounds 35 being administered in an amount that is effective to treat, prevent or delay the onset of type 2 diabetes.

In accordance with the methods described herein one method that is of interest relates to a method of treating a condition selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, and other conditions and disorders where insulin resistance is a component, in a mammalian patient in need of such treatment, comprising administering to the patient an effective amount of a compound of formula I and a compound selected from the group consisting of: (a) DP-IV inhibitors; (b) insulin sensitizers selected from the group consisting of (i) PPAR agonists and (ii) biguanides; (c) insulin and insulin mimetics; (d) sulfonylureas and other insulin secretagogues; (e) alpha glucosidase inhibitors; (f) glucagon receptor antagonists; (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; (h) GIP, GIP mimetics, and GIP receptor agonists; (i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists; (j) cholesterol lowering agents selected from the group consisting of: (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinic alcohol, nicotinic acid and salts thereof, (iv) PPAR alpha agonists, (v) PPARalpha/gamma dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, (viii) anti-oxidants and (ix) LXR modulators; (k) PPAR delta agonists; (l) antiobesity compounds; (m) an ileal bile acid transporter inhibitor; (n) anti-inflammatory agents excluding glucocorticoids; and (o) protein tyrosine phosphatase-1B (PTP-1B) inhibitors,

said compounds being administered to the patient in an amount that is effective to treat said condition.

More particularly, a method that is of interest relates to a method of treating a condition selected from the group consisting of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia and dyslipidemia, in a mammalian patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a compound of formula I and an HMG-CoA reductase inhibitor.

Even more particularly, the method that is of interest comprises administering to the patient a therapeutically effective amount of a compound of formula I and an HMG-CoA reductase inhibitor wherein the HMG-CoA reductase inhibitor is a statin, and even more particularly, the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

A different aspect of the invention relates to a method of reducing the risk of developing a condition selected from the group consisting of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia and dyslipidemia, and the sequelae of such

conditions comprising administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of formula I and an HMG-CoA reductase inhibitor.

Another aspect of the invention relates to a method for delaying the onset or reducing the risk of developing atherosclerosis in a human patient in need of such treatment comprising administering to said patient an effective amount of a compound of formula I and an HMG-CoA reductase inhibitor. More particularly, the method comprises administering an effective amount of a compound of formula I and an HMG-CoA reductase inhibitor wherein the HMG-CoA reductase inhibitor is a statin. Even more particularly, the method comprises administering a compound of formula I and a statin selected from the group consisting of: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin. Still more particularly, the method comprises administering a compound of formula I and the statin known as simvastatin.

Another aspect of the invention relates to a method of reducing the risk of developing a condition selected from the group consisting of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia and dyslipidemia, and the sequelae of such conditions comprising administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of formula I and a cholesterol absorption inhibitor. In particular, the method comprises administering an effective amount of a compound of formula I and the cholesterol absorption inhibitor known as ezetimibe.

More particularly, a method for delaying the onset or reducing the risk of developing atherosclerosis in a human patient in need of such treatment is described which comprises administering to said patient an effective amount of a compound of formula I and a cholesterol absorption inhibitor. More particularly, the method comprises administering a compound of formula I and the cholesterol absorption inhibitor known as ezetimibe.

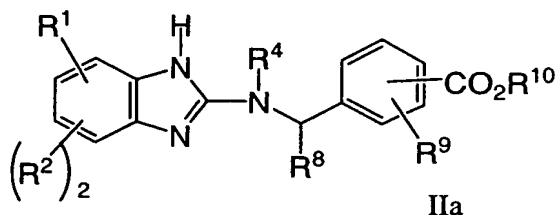
Throughout the instant application, the following abbreviations are used with the following meanings unless otherwise indicated:

Bu = butyl, t-Bu = t-butyl	Bn and Bnzl = benzyl
BOC, Boc = t-butyloxycarbonyl	CBZ, Cbz = Benzyloxycarbonyl
DCC = Dicyclohexylcarbodiimide	DCM = dichloromethane
DIEA = diisopropylethylamine	DMF = N,N-dimethylformamide
DIAD = diisopropylazodicarboxylate	Et = ethyl
DMAP = 4-Dimethylaminopyridine	EtOH = ethanol
EtOAc = ethyl acetate	FAB-mass spectrum = Fast atom bombardment-mass spectroscopy
eq. = equivalent(s)	HPLC = High pressure liquid chromatography
HOAc = acetic acid	LAH = Lithium aluminum hydride

HOBT, HOBt = Hydroxybenztriazole	PBS = phosphate buffer saline
Me = methyl	TFA = Trifluoroacetic acid
Ph = phenyl	TMS = Trimethylsilane
THF = Tetrahydrofuran	Nme ₂ = dimethylamino
C ₆ H ₁₁ = cyclohexyl	2ClPh = 2-chlorophenyl
iPr, ⁱ Pr = isopropyl	Py, Pyr = pyridyl
2,4-diClPh = 2,4-dichlorophenyl	

Compounds of the present invention may be prepared according to the methodology outlined in the following general synthetic schemes.

5 In one embodiment of the present invention, the compounds (Ia) where R³ is hydrogen may be prepared from ester IIa (*vide infra*),



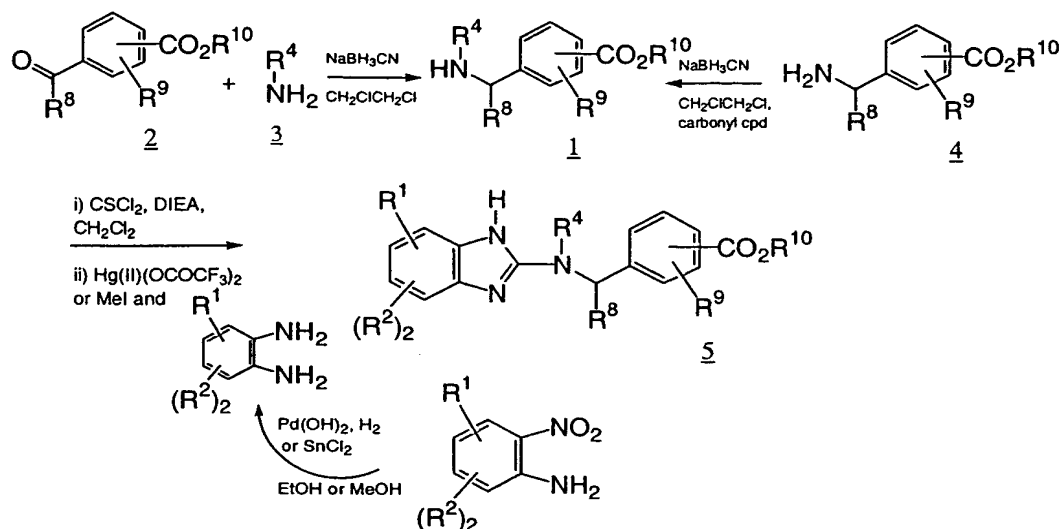
where R¹, R², R⁴, R⁸, and R⁹ are as defined above and R¹⁰ represents an alkyl or aryl group.

10 Compounds IIa are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art as described in "Comprehensive Organic Chemistry", Katritzky et. al., Vol 5. One such route is illustrated in Scheme 1. Amine 1 may be commercially available or readily prepared via a reductive amination sequence by treating, for example, carbomethoxy benzaldehyde 2 (if R⁸ and R⁹ are hydrogen) and an amine 3 with a reducing agent such as sodium triacetoxymethylborohydride or cyanoborohydride in a solvent such as dichloroethane at ambient temperature. Alternatively, the benzylamine 4 can be reacted with the appropriate R⁴ carbonyl containing substituent under the same conditions to give amine 1. Amine 1 is then treated with thiophosgene in the presence of a base such as diethylisopropylamine (DIEA) in a nonpolar aprotic solvent such as dichloromethane at temperatures of zero to 25° C followed by direct addition of a 1,2-diaminobenzene and either mercury (II) trifluoroacetate or methyl iodide (for example *J. Med. Chem.*, 1985, 28, 1925 and *Synthesis*, 1974, 41). The reaction is stirred a further 30 min to 6h before isolation of benzimidazole 5 with an aqueous work-up. 1,2-Diaminobenzene analogs are commercially available, or readily prepared by those skilled in the art by reduction of the corresponding 2-nitroaniline with, for example hydrogen and a palladium catalyst or stannous chloride. Either reaction is effected in an alcoholic solvent such as methanol or ethanol.

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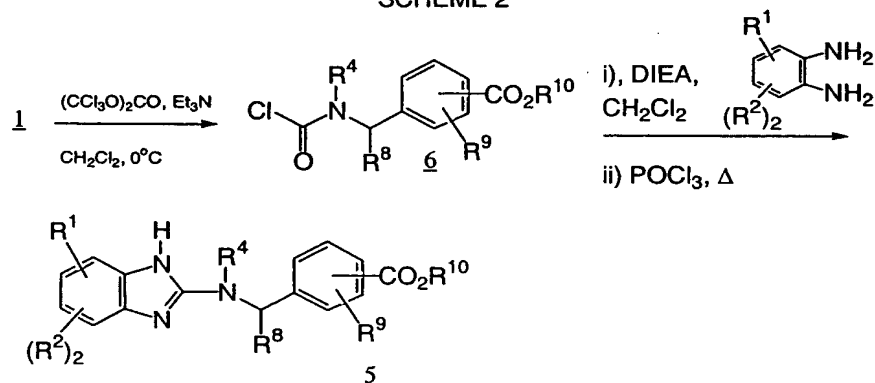
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SCHEME 1



An alternative approach to synthesizing benzimidazole **IIa** involves reaction of amine **1** with triphosgene in the presence of a base, such as triethylamine, in a nonpolar aprotic solvent such as dichloromethane at temperatures of zero to 25°C, as shown in Scheme 2. The carbamoyl chloride **6** formed in the reaction can be readily isolated and treated with a 1,2-diaminobenzene to give the urea which is treated directly with a dehydrating agent, usually phosphorus oxychloride, at elevated temperatures for 6 - 24h, followed by an aqueous work-up to yield the benzimidazole **5**.

SCHEME 2

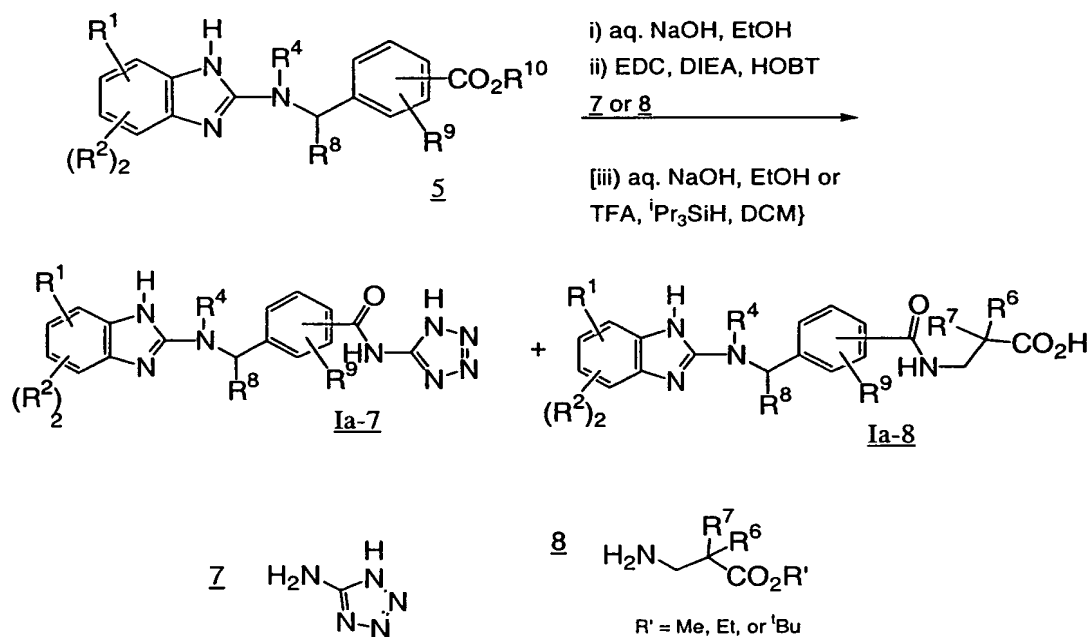


Preparation of the desired compounds **Ia** (which are defined as compounds of formula **I** wherein R^3 represents H) is then achieved by saponification of the ester **5** using a base such as aqueous lithium or sodium hydroxide in a polar solvent such as tetrahydrofuran, methanol, ethanol or a mixture of similar solvents, Scheme 3. Coupling of the acid with an amine, generally 5-aminotetrazole **7** or a beta alanine derivative **8** which may be substituted at the 2-position, is then achieved using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), 1-hydroxybenzotriazole (HOBt), and a base, generally

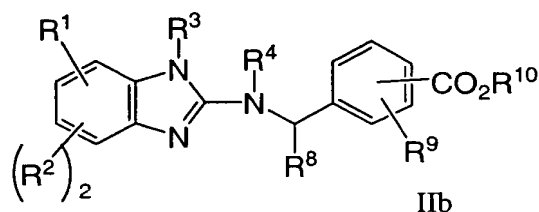
diisopropylethylamine, in a solvent such as N,N-dimethylformamide (DMF) or methylene chloride for 3 to 48 hours at ambient temperature to yield the compounds Ia-7 and Ia-8. Other peptide coupling conditions may also be used. The product is purified from unwanted side products by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still et al, *J. Org. Chem.*, 43, 2923, (1978), or HPLC. Compounds purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner. As will be understood by those skilled in the art, for the preparation of enantiomerically pure compounds, enantiomerically pure starting materials should be used.

In some cases further modification of intermediates such as 5 can be undertaken in one of several different ways. These manipulations may include, but are not limited to substitution, reduction, oxidation, alkylation, acylation, and hydrolysis reactions, which are commonly known to those skilled in the art.

SCHEME 3



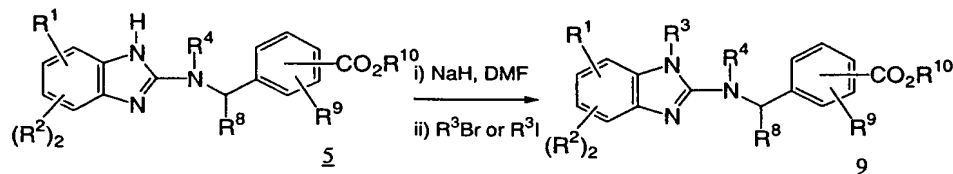
In another embodiment of the present invention, the compounds (Ib) (which are defined as compounds of formula I wherein R^3 is not hydrogen) may be prepared from ester IIb (*vide infra*),



where R^1, R^2, R^3, R^4, R^8 , and R^9 are as defined above and R^{10} represents an alkyl or aryl group.

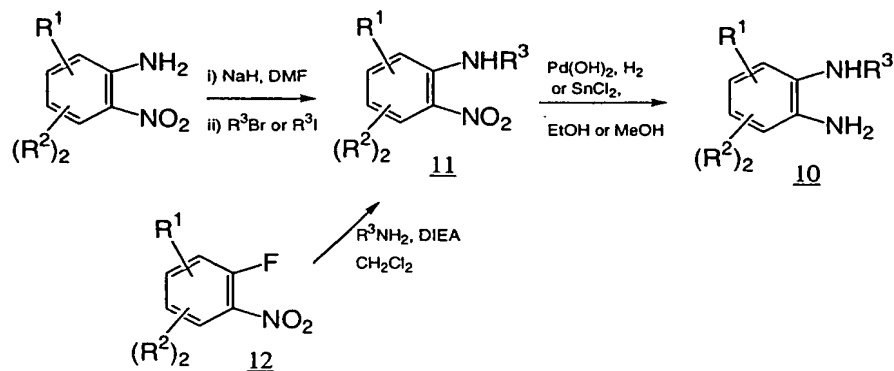
Compounds **IIb** may be conveniently prepared by a variety of methods known to those skilled in the art. One such example, shown in Scheme 4, involves alkylation of intermediate **5** by deprotonation with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide (DMF) at 0 – 25 °C for 15min to 2h, followed by addition of an electrophile such as an alkyl iodide. The reaction is stirred, with heating if necessary, for an additional 1 - 24 h to give intermediate **9**.

SCHEME 4

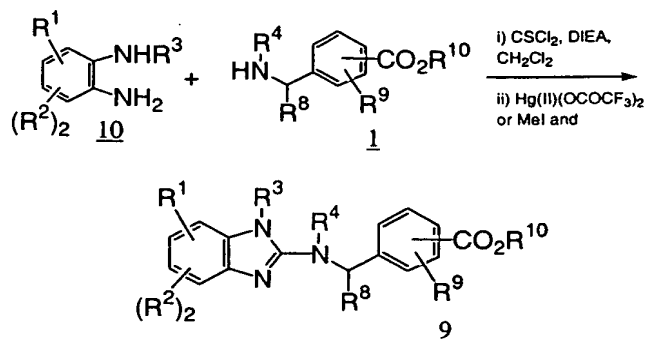


An alternative route goes via the N-alkylated 1,2-diaminobenzene **10**. These are commercially available or readily prepared by those skilled in art. One such method involves alkylation of a 2-nitro aniline. This is effected by deprotonation with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide (DMF) at 0 – 25 °C for 15min to 2h, followed by addition of an electrophile such as an alkyl iodide, Scheme 5. The reaction is stirred for an additional 1 – 24 h to give intermediate **11**, which can be reduced with, for example hydrogen and a palladium catalyst or stannous chloride in an alcoholic solvent. The alkylated 2-nitro aniline **11** can also be prepared by nucleophilic displacement of fluorine from a 2-fluoronitrobenzene **12** with an amine as described in *J. Org. Chem.*, 1999, 64, 3060. This is achieved in a solvent such as methylene chloride or DMF with a base such as DIEA, at temperatures of 25 – 80 °C for 1-6h, Scheme 5. The diaminobenzene **10** can then be converted to the benzimidazole **9** using amine **1** or carbamoyl chloride **6** in an identical fashion to that described above and illustrated in Schemes 6 and 7.

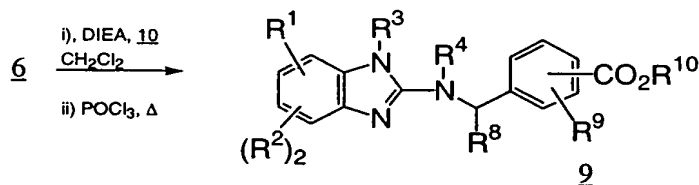
SCHEME 5



SCHEME 6

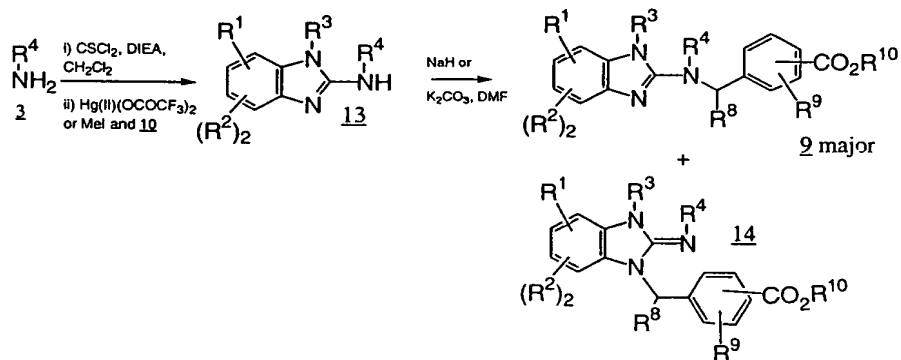


SCHEME 7

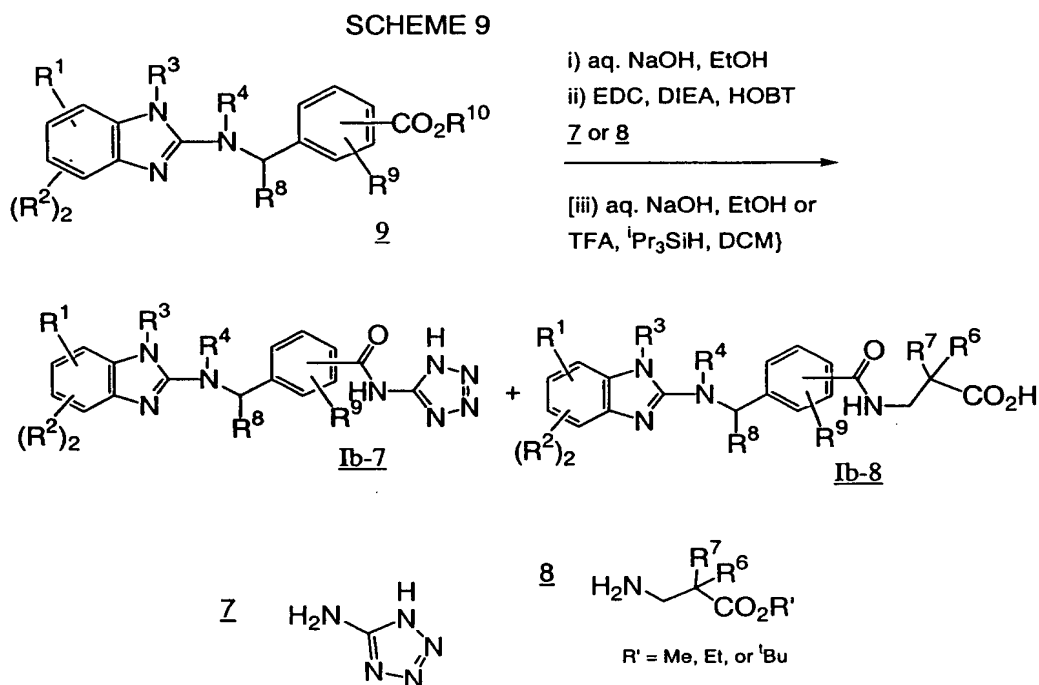


A third route to intermediates **IIb** involves alkylation of the 2-aminobenzimidazole **13** with a benzylic bromide, for example carbomethoxybenzyl-bromide, as illustrated in Scheme 8. Amine **3** is converted to the isothiocyanate by reaction with thiophosgene in the presence of a base such as DIEA in a nonpolar aprotic solvent such as dichloromethane at temperatures of zero to 25° C followed by addition of diamine **10** and cyclization with an agent such as methyl iodide. This reaction is effected at 25 – 50 °C for 1 – 24 h to give amine **13**. Deprotonation is achieved with a base such as sodium hydride or potassium carbonate in a nonpolar aprotic solvent such as DMF to give a mixture of the desired compound **9** and its isomer **14**. These are generally separable by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel or HPLC.

SCHEME 8



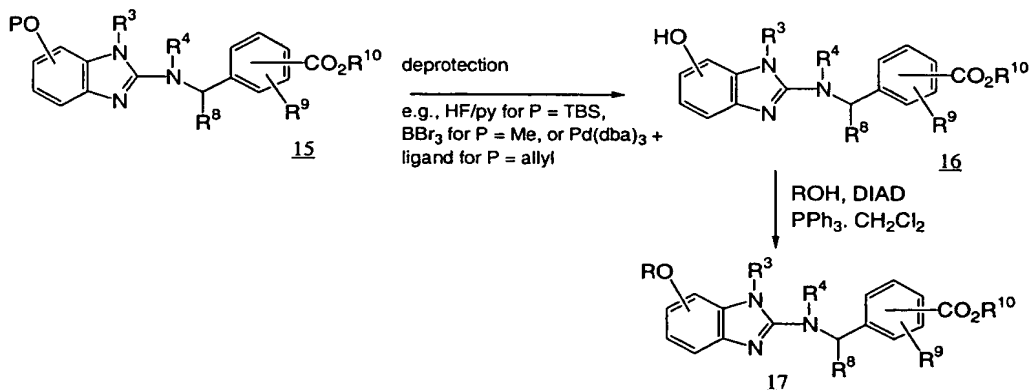
Conversion of ester 9 to the final products is achieved by saponification of the ester using a base such as aqueous lithium or sodium hydroxide in a polar solvent such as tetrahydrofuran, methanol, ethanol or a mixture of similar solvents, Scheme 9. Coupling of the acid with an amine, generally 5-aminotetrazole 7 or a beta alanine derivative 8 which may be substituted at the 2-position, is then achieved using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), 1-hydroxybenzotriazole (HOBt), and a base, generally diisopropylethylamine, in a solvent such as N,N-dimethylformamide (DMF) or methylene chloride for 3 to 48 hours at ambient temperature to yield the compounds Ib-7 and Ib-8. Other standard peptide coupling conditions may also be used. The product is purified from unwanted side products by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still et al, *J. Org. Chem.*, 43, 2923, (1978), or HPLC. Compounds purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.



In some cases further modification of intermediates such as 9 can be undertaken in one of several different ways. These manipulations may include, but are not limited to substitution, reduction, oxidation, alkylation, acylation, and hydrolysis reactions, which are commonly known to those skilled in the art. One such modification, illustrated here when R^1 or R^2 is a protected alcohol as in 15, involves release of the alcohol and subsequent etherification. The hydroxyl group may be protected as a silyl ether, in which case a fluoride source, generally hydrofluoric acid or tetrabutylammonium fluoride is used for the reaction. Deprotection of a methoxy ether is routinely effected by treatment of the compound with boron tribromide in a solvent such as methylene chloride for a period of 1 – 16h at

ambient temperatures. Finally, if the alcohol is protected as an allyl ether, this is removed by treatment with dimethylbarbituric acid and a palladium catalyst, routinely tris(dibenzylideneacetone)dipalladium(0), with a ligand such as 1,4-bis-(diphenylphosphino)butane in an aprotic solvent such as methylene chloride for 15min to 2h. See "Protective Groups in Organic Synthesis", Greene, published by Wiley and Sons.

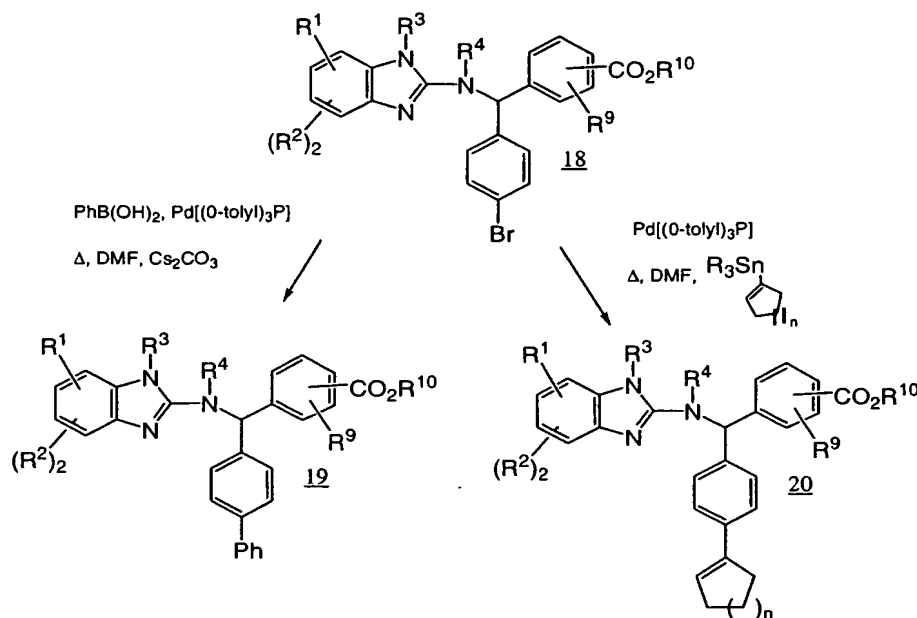
SCHEME 10



The free hydroxyl group may then be further modified to prepare ethers using an alcohol and coupling agent, such as diisopropylazodicarboxylate, and triphenylphosphine in a non polar solvent such as methylene chloride at temperatures of 0 to 40°C for 1 to 16h, Scheme 10. Intermediates **16** and **17** can then be converted to the desired products as previously described, *vide supra*.

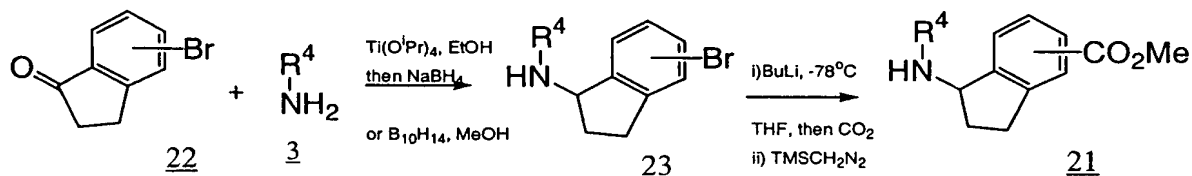
Another such modification, illustrated here when R⁴ contains an aromatic halide as in **18**, Scheme 11, involves coupling reactions either with a boronic acid in a Suzuki type coupling or a vinyl stannane to give products such as **19** and **20**. For the former reaction, the halide is coupled with a boronic acid, exemplified here with phenyl boronic acid, using a palladium catalyst such as palladium acetate and tris-o-tolylphosphine or triphenyl phosphine. The solvent is generally DMF or ethanol, and cesium carbonate or aqueous sodium carbonate is also added to the reaction, which is performed at elevated temperatures for 12-24 h (see *Helv. Chim. Acta*, 1992, 75, 855). Preparation of intermediates **20** is carried out by reaction with a vinyl stannane in the presence of a palladium catalyst such as palladium tris-o-tolylphosphine. The solvent is generally DMF, and the reaction is performed at elevated temperatures for 1-8 h. Intermediates **19** and **20** can then be converted to the desired products as previously described, *vide supra*.

SCHEME 11



In cases where R^8 and R^9 form a 5-membered ring alternate conditions were used for the synthesis of the amine intermediate **21**, Scheme 12. For example, commercially available ketone **22** was converted to amine **23** by a reductive amination sequence using a Lewis acid such as titanium isopropoxide in ethanol at ambient temperature for 6 – 24 h, followed by further reduction with a hydride reducing agent such as sodium borohydride (J. C. S., Perkin Trans 1, 1998, 2527-2531). Alternatively, decaborane in methanol at ambient temperature can be used for the reductive amination (J.C.S. Perkin Trans 1, 2000 145-146). The requisite ester linkage is then installed by treatment of the bromide with a base such as butyl lithium at -78°C in a polar aprotic solvent such as THF, followed by quenching the reaction with solid carbon dioxide to give the acid. Esterification, with TMS diazomethane for example, gives amine **21**. Intermediate **21** can then be converted to the desired products as previously described, *vide supra*.

SCHEME 12



The following examples are provided so that the invention might be more fully understood. They should not be construed as limiting the invention in any way.

General experimental: Analytical HPLC analysis for examples 1 – 274 (HPLC A) was performed on a YMC Combiscreen ODS-A column (50 x 4.6 mm i.d.) at a flow rate of 4 mL/min using a gradient elution of 10 – 100% acetonitrile in water containing 0.1% trifluoroacetic acid. Preparative HPLC was performed on a YMC-Pack Pro C18 column (150 x 20 mm i.d.) at an initial flow rate of 4 mL/min for 1.35 min, followed by 20 mL/min for 10.6min. Various concentration gradients were used during the faster part of the run (see below), and all runs were followed with 100% organic for 0.5 min.

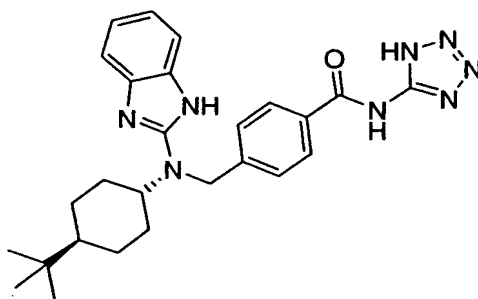
Condition A: 10 to 90% acetonitrile in water (each containing 0.1% trifluoroacetic acid).

Condition B: 20 to 60% acetonitrile in water (each containing 0.1% trifluoroacetic acid).

Condition C: 20 to 80% acetonitrile in water (each containing 0.1% trifluoroacetic acid).

Condition D: 20 to 100% acetonitrile in water (each containing 0.1% trifluoroacetic acid).

EXAMPLE 1



Step A. 1-Isothiocyanato-2-nitrobenzene.

To a solution of 2-nitroaniline (10 mmol, 1.38 g) and DIEA (15 mmol, 2.6 mL) in 10 mL of DCM at 0°C was added thiophosgene (15 mmol, 1.14 mL). The reaction was brought to 65° for 45 min. Purification by flash chromatography on silica eluting with 10% EtOAc/hexanes afforded the isothiocyanate as a gold solid. HPLC A: 2.24 min.

Step B. Methyl 4-[[4-(4-tert-butylcyclohexyl)amino]methyl]benzoate

To a solution of methyl-4-formylbenzoate (73 mmol, 12 g) in 200 mL of MeOH was added 4-tert-butylcyclohexylamine (74 mmol, 13.2 mL) via syringe. The reaction mixture was heated to reflux for 0.75 h, then was cooled in an ice bath. The resulting precipitate was filtered and the filter cake was washed with 2 x 20 mL of cold MeOH. The solid was dried under reduced pressure, then suspended in 224 mL of MeOH. HOAc (652 mmol, 37.4 mL) was added to the solution, followed by NaBH₃CN (42.7 mmol, 2.68 g) in several portions. The reaction mixture was stirred at ambient temperature for 1.5 h, then concentrated under reduced pressure to ca. 25 % of the initial volume. 400 mL of EtOAc was added to the solution and the mixture was washed with 3 x 200 mL of 5 % NaHCO₃ followed by brine. The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 1:1 EtOAc/hexanes to afford the trans isomer as a

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white solid. ¹H NMR (500 MHz, CDCl₃): δ 8.00 (d, 2H), 7.40 (d, 2H), 3.92 (s, 3H), 3.88 (s, 2H), 2.40 (m, 1H), 2.01 (m, 2H), 1.79 (m, 2H), 0.95 – 1.15 (overlapping m, 5H), 0.85 (s, 9H).

Step C. Methyl 4-([1H-benzimidazol-2-yl](4-*tert*-butylcyclohexyl)amino)methyl)-benzoate

5 To the title compound of Example 1 Step B (2.13 mmol, 721 mg) in 2.5 mL of DMF was added DIEA (0.8 mL), followed by the title compound of Example 1 Step A (2.5 mmol, 450 mg). The reaction mixture was concentrated under reduced pressure. The residue was taken up in 5 mL of DMF containing 0.4 mL of H₂O, and SnCl₂ (2 g) was added (exothermic). The crude thiourea was concentrated under reduced pressure and the residue was taken up in 10 mL of EtOH. MeI (400 μL) was added and
10 the resulting mixture was heated at 60° for 1 h and concentrated under reduced pressure. The product was purified by flash chromatography on silica eluting with 30% EtOAc/hexanes affording a slightly pink solid. ¹H NMR (500 MHz, CD₃OD): δ 8.00 (d, 2H), 7.43 (d, 2H), 7.29 (m, 2H), 7.14 (m, 2H), 4.86 (s, 2H), 4.04 (m, 1H), 3.89 (s, 3H), 1.82 – 1.95 (overlapping m, 4H), 1.57 (m, 2H), 1.29 (m, 2H), 1.05 (m, 1H), 0.89 (s, 9H). MS (ESI): m/z 420 (M + H). HPLC A: 2.30 min.

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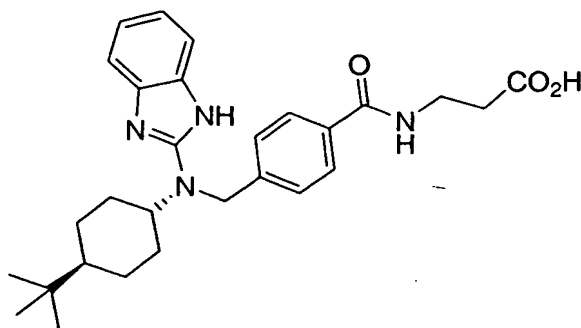
Step D. 4-([1H-Benzimidazol-2-yl](4-*tert*-butylcyclohexyl)amino)methyl)benzoic acid

To the title compound of Example 1 Step C (0.21 mmol, 90 mg) in 2 mL of dioxane was added a solution of LiOH (2.1 mmol, 52 mg) in 0.6 mL of H₂O. The reaction was stirred at 40°C for 3 h. The product was partitioned into EtOAc/H₂O acidified with 2 N HCl. The aqueous phase was washed
20 with EtOAc and the combined organic phase was dried with MgSO₄ and concentrated under reduced pressure affording a yellow solid. HPLC A: 1.98 min.

Step E. 4-([1H-Benzimidazol-2-yl](4-*tert*-butylcyclohexyl)amino)methyl)-N-(1H-tetra-azol-5-yl)benzamide

25 To a solution of the title compound of Example 1 Step D (0.1 mmol, 41 mg), 1H-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), HOBT (0.25 mmol, 38 mg) and EDC (0.4 mmol, 77 mg) in 1 mL of DMF was added DIEA (0.5 mmol, 90 μL). The reaction mixture was allowed to stand at ambient temperature overnight, then concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/H₂O, acidified with TFA, and purified by reverse-phase chromatography (Condition A).
30 Lyophilization afforded the product as a white solid. MS (ESI): m/z 473 (M + H). HPLC A: 1.86 min.

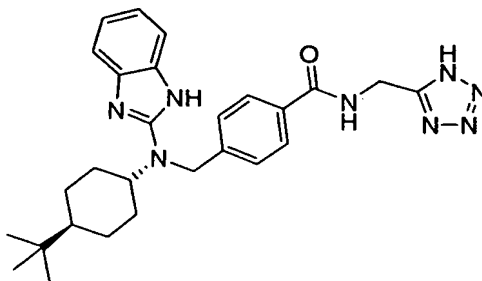
EXAMPLE 2



N-(4-([1H-Benzimidazol-2-yl(4-tert-butylcyclohexyl)amino)methyl]benzoyl)-β-alanine

To a solution of the title compound of Example 1 Step D (0.1 mmol, 41 mg), the hydrochloride salt of β-alanine tert-butyl ester (0.15 mmol, 27 mg), HOBt (0.25 mmol, 38 mg) and EDC (0.4 mmol, 77 mg) in 1 mL of DMF was added DIEA (0.5 mmol, 90 μL). The reaction mixture was allowed to stand at ambient temperature overnight, then partitioned into EtOAc/H₂O. The aqueous phase was washed with EtOAc, and the combined organic phase was dried with MgSO₄ and the solvent was removed under reduced pressure. The residue was treated with 3 mL of 2:30:68 H₂O/TFA/DCM for 1 hr and the solution was concentrated under reduced pressure. Purification by reverse-phase chromatography (Condition A), followed by lyophilization, afforded the product as a white solid. MS (ESI): m/z 477 (M + H). HPLC A: 1.70 min.

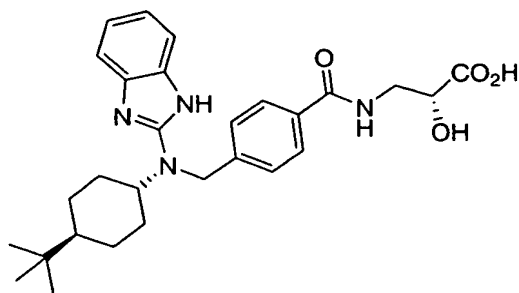
EXAMPLE 3



4-([1H-Benzimidazol-2-yl(4-tert-butylcyclohexyl)amino)methyl]-N-(1H-tetrazol-5-ylmethyl)benzamide

To a solution of the title compound of Example 1 Step D (0.04 mmol, 16 mg), 1H-tetrazol-5-ylmethylamine (0.06 mmol, 8 mg), HOBt (0.1 mmol, 15 mg) and EDC (0.12 mmol, 23 mg) in 0.4 mL of DMF was added DIEA (0.2 mmol, 35 μL). After 3 h the reaction mixture was concentrated under reduced pressure. The product was purified by reverse-phase chromatography (Condition A) and lyophilized, affording the title compound as a white solid. MS (ESI): m/z 487 (M + H). HPLC A: 1.58 min.

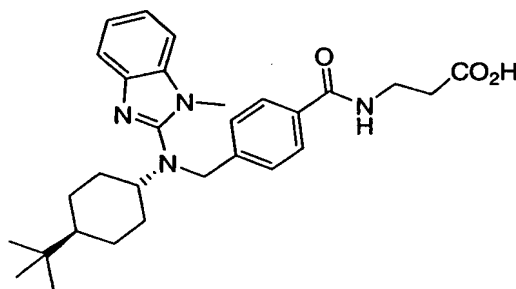
EXAMPLE 4



(2R)-3-[(4-[[1H-Benzimidazol-2-yl](4-tert-butylcyclohexyl)amino]methyl)benzoyl]-amino]-2-hydroxypropanoic acid

- 5 To a solution of the title compound of Example 1 Step D (0.04 mmol, 16 mg), the hydrochloride salt of 2-hydroxy β -alanine methyl ester (0.06 mmol, 9 mg), HOBt (0.1 mmol, 15 mg), and EDC (0.12 mmol, 23 mg) in 0.4 mL of DMF was added DIEA (0.2 mmol, 35 μ L). After 3 h the reaction was partitioned into EtOAc/brine. The organic phase was dried with MgSO_4 and concentrated under reduced pressure. The residue was taken up in 1 mL of dioxane and a solution of LiOH (1 mmol, 24 mg)
- 10 in 0.5 mL of H_2O was added. The reaction was stirred at ambient temperature overnight, acidified with TFA and the product was purified by reverse-phase chromatography (Condition A) and lyophilized, affording the title compound as a white solid. MS (ESI): m/z 493 ($M + H$). HPLC A: 1.73 min.

EXAMPLE 5



15

Step A. 4-[[[(4-tert-Butylcyclohexyl)(1-methyl-1H-benzimidazol-2-yl)amino]methyl]-benzoic acid

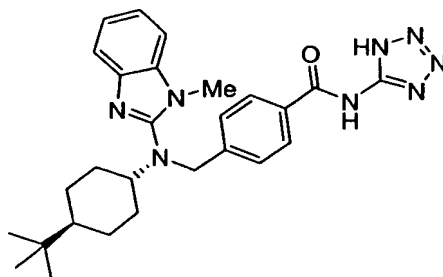
- To the title compound from Example 1 Step C (0.72 mmol, 300 mg) in 5 mL of THF was added MeI (1 mmol, 67 μ L), followed by NaH (1 mmol, 40 mg of 60% dispersion in mineral oil)
- 20 (exothermic, H_2 evolution). After 1 h starting benzimidazole was still present, so the reaction was treated with additional MeI (1 mmol) and NaH (1 mmol). After 1 h the reaction was complete (HPLC A: 2.38). The mixture was concentrated under reduced pressure and the residue was taken up in 6 mL of dioxane.

A solution of LiOH (7 mmol, 172 mg) in 2 mL of H₂O was added and the resulting mixture was stirred at ambient temperature overnight. The mixture was poured into EtOAc/ H₂O, and acidified with 2 N HCl until two clear layers formed after agitation. The organic layer was collected and the aqueous layer was washed with EtOAc. The combined organic phase was dried with MgSO₄ and concentrated under reduced pressure affording product as a yellow solid. MS (ESI): m/z 420 (M + H). HPLC A: 2.09 min.

Step B. N-(4-[[[(4-*tert*-Butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]-benzoyl]-β-alanine

To a solution of the title compound of Example 5 Step A (0.06 mmol, 24 mg), the hydrochloride salt of β-alanine *tert*-butyl ester (0.09 mmol, 16 mg), HOBt (0.15 mmol, 23 mg) and EDC (0.18 mmol, 35 mg) in 0.8 mL of DCM was added DIEA (0.3 mmol, 52 μL). The reaction mixture was allowed to stand at ambient temperature for 3 h, then partitioned into EtOAc/brine. The aqueous phase was washed with EtOAc, and the combined organic phase was dried with MgSO₄ and the solvent was removed under reduced pressure. The residue was treated with 3 mL of 2:30:68 H₂O/TFA/DCM for 1 hr and the solution was concentrated under reduced pressure. The crude product was purified by reverse-phase chromatography (Condition A), then lyophilized, affording the title compound as a white solid. MS (ESI): m/z 491 (M + H). HPLC A: 1.92 min.

EXAMPLE 6

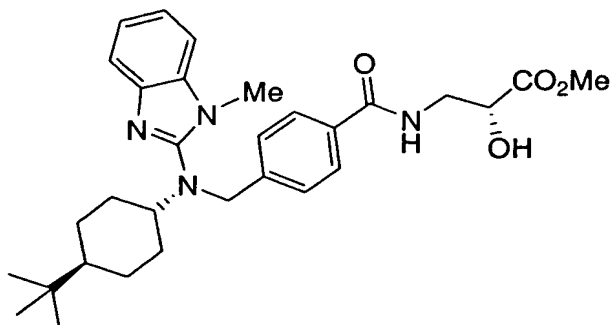


4-[[[(4-*tert*-Butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]-N-(1*H*-tetraazol-5-yl)benzamide

To a solution of the product of Example 5 Step A (0.14 mmol, 64 mg), 1*H*-tetraazol-5-amine monohydrate (0.28 mmol, 29 mg), HOBt (0.35 mmol, 53 mg) and EDC (0.56 mmol, 108 mg) in 1 mL of DMF was added DIEA (0.7 mmol, 122 μL). The reaction was allowed to stand at ambient temperature for 21 h, then concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/ H₂O and acidified with TFA, then purified by reverse-phase chromatography (Condition A). The product was lyophilized, affording a white solid. ¹H NMR (500 MHz, CD₃OD): δ 8.01 (d, 2H), 7.52 – 7.62 (overlapping m, 3H), 7.35 – 7.50 (overlapping m, 3H), 3.87 (s, 3H), 3.76 (m, 1H), 2.16 (m, 2H),

1.99 (m, 2H), 1.84 (m, 2H), 1.30 (m, 2H), 1.14 (m, 1H), 0.92 (s, 9H). MS (ESI): m/z 487 (M + H). HPLC A: 1.97 min.

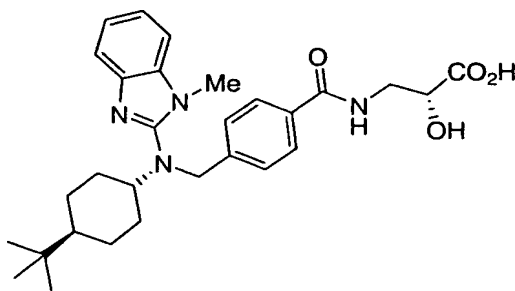
EXAMPLE 7



5 Methyl (2R)-3-[(4-[[4-*tert*-butylcyclohexyl](1-methyl-1*H*-benzimidazol-2-yl)amino]methyl}benzoyl)amino]-2-hydroxypropanoate

To a solution of the title compound of Example 5 Step A (0.32 mmol, 145 mg), the hydrochloride salt of 2-hydroxy β -alanine methyl ester (0.48 mmol, 74 mg), HOBt (0.8 mmol, 121 mg) and EDC (0.96 mmol, 183 mg) in 2 mL of DMF was added DIEA (1.6 mmol, 0.28 mL). After 3 h the reaction was partitioned into EtOAc/brine. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash chromatography on silica eluting with 1:25:74 MeOH/EtOAc/DCM, affording the title compound as a foamy solid. 1H NMR (500 MHz, $DMSO-d_6$): δ 8.47 (t, 1H), 7.75 (d, 2H), 7.60 (m, 1H), 7.48 (m, 1H), 7.45 (d, 2H), 7.30 – 7.37 (overlapping m, 2H), 4.80 (s, 2H), 3.76 (s, 3H), 3.70 (m, 1H), 3.60 (s, 3H), 3.50 (m, 1H), 3.39 (m, 1H), 2.02 (m, 2H), 1.82 (m, 2H), 1.71 (m, 2H), 1.18 (m, 2H), 1.03 (m, 1H), 0.85 (s, 9H). MS (ESI): m/z 521 (M + H). HPLC A: 1.94 min.

EXAMPLE 8

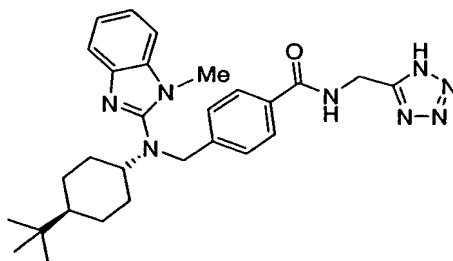


20 (2R)-3-[(4-[[4-*tert*-Butylcyclohexyl](1-methyl-1*H*-benzimidazol-2-yl)amino]methyl}benzoyl)amino]-2-hydroxypropanoic acid

To a solution of the title compound of Example 7 (0.1 mmol, 50 mg) in 2 mL of MeOH was added LiOH (0.5 mmol, 12 mg). H_2O was added dropwise until the reaction became slightly cloudy,

then the mixture was sonicated to dissolve the LiOH. The reaction was stirred at 40°C for 2 h. The reaction was concentrated under reduced pressure and the residue was taken up in dioxane/H₂O and acidified with TFA. Purification by reverse-phase HPLC (Condition A), followed by lyophilization, afforded the title compound as a white solid. ¹H NMR (500 MHz, CD₃OD): δ 7.79 (d, 2H), 7.58 (m, 1H), 7.39 – 7.52 (overlapping m, 5H), 4.86 (s, 2H), 4.34 (m, 1H), 3.87 (s, 3H), 3.52 – 3.84 (overlapping m, 3H), 2.16 (m, 2H), 1.99 (m, 2H), 1.84 (m, 2H), 1.31 (m, 2H), 1.14 (m, 1H), 0.92 (s, 9H). MS (ESI): m/z 487 (M + H). MS (ESI): m/z 507 (M + H). HPLC A: 1.84 min.

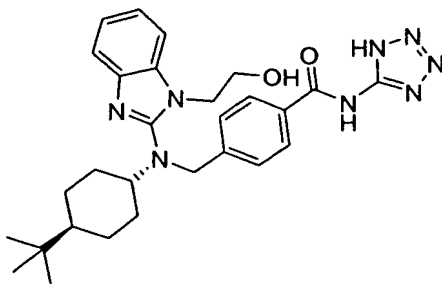
EXAMPLE 9



4-[[[(4-*tert*-Butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]-*N*-(1*H*-tetrazol-5-ylmethyl)benzamide

To a solution of the title compound of Example 5 Step A (0.06 mmol, 25 mg) 1*H*-tetrazol-5-ylmethylamine (0.09 mmol, 12 mg), HOBt (0.15 mmol, 23 mg) and EDC (0.18 mmol, 35 mg) in 0.5 mL of DMF was added DIEA (0.3 mmol, 52 μL). The reaction was allowed to proceed overnight at ambient temperature. The mixture was partitioned between EtOAc/brine. The organic phase was concentrated under reduced pressure and the residue was purified by reverse-phase chromatography (Condition A) and lyophilized, affording the title compound as a white solid. MS (ESI): m/z 517 (M + H). HPLC A: 1.94min.

EXAMPLE 10



Step A. Methyl 4-({[(4-*tert*-butylcyclohexyl)(1-{2-[(trimethylsilyl)oxy]ethyl}-1*H*-benzimidazol-2-yl)amino]methyl}benzoate

To the title compound from Example 1 Step C (0.5 mmol, 210 mg) in 1 mL of THF was added a solution of NaH (1 mmol, 40 mg of 60% slurry in mineral oil) in 1 mL of DMF (exothermic, H₂ evolution). After gas evolution ceased for several minutes, (2-bromoethoxy)(trimethyl)silane was added to the solution via syringe. The reaction mixture was heated to 40°C. After 2.5 h the reaction was quenched by addition of saturated ammonium chloride. The product was extracted 3x with EtOAc and the organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica eluting with 5 % EtOAc/hexanes. HPLC A: 3.14 min.

Step B. 4-({[(4-*tert*-Butylcyclohexyl)(1-{2-hydroxyethyl}-1*H*-benzimidazol-2-yl)-amino]methyl}benzoic acid

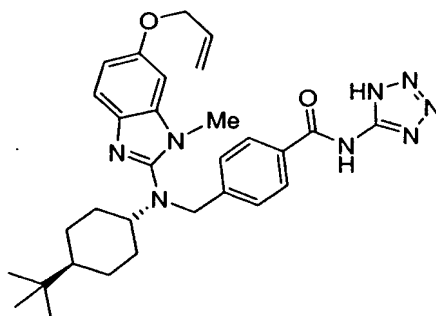
To the title compound of Example 10 Step A (0.13 mmol, 73 mg) in 2 mL of dioxane was added a solution of LiOH (1.25 mmol, 30 mg) in 1 mL of H₂O. The resulting solution was stirred at 40°C overnight. The reaction mixture was taken up in a pH 7 buffer solution and EtOAc. The mixture was acidified with 2 N HCl until two clear layers formed after agitation. The organic layer was collected and the aqueous layer was washed with EtOAc. The combined organic layers were dried with MgSO₄ and concentrated under reduced pressure to afford the acid as a beige solid. MS (ESI): m/z 450 (M + H). HPLC A: 2.05 min.

Step C. 4-({[(4-*tert*-Butylcyclohexyl)[1-(2-hydroxyethyl)-1*H*-benzimidazol-2-yl]amino}-methyl)-*N*-(1*H*-tetraazol-5-yl)benzamide

To a solution of the title compound of Example 10 Step B (0.04 mmol, 19 mg) 1*H*-tetraazol-5-amine monohydrate (0.13 mmol, 13 mg), HOBt (0.085 mmol, 13 mg) and EDC (0.17 mmol, 33 mg) in 0.5 mL of DMF was added DIEA (0.21 mmol, 36 µL). The reaction mixture was allowed to stand at ambient temperature overnight, then concentrated under reduced pressure. The residue was

taken up in ca. 2:1 dioxane/H₂O and acidified with TFA, then purified by reverse-phase chromatography (Condition B). The product was lyophilized, affording the title compound as a white solid. MS (ESI): *m/z* 517 (M + H). HPLC A: 1.81 min.

EXAMPLE 11



Step A. 4-Allyloxy-2-fluoro-nitrobenzene

To a solution of 3-fluoro-4-nitrophenol (17.5 mmol, 2.75 g) and allyl bromide (17.5 mmol, 1.5 mL) in 10 mL of DMF was added K₂CO₃ (21 mmol, 2.9 g). The slurry was stirred at ambient temperature overnight, and partitioned into NaHCO₃ (aq)/DCM. The organic phase was removed under reduced pressure affording the product as a brown oil. HPLC A: 2.19 min.

Step B. 5-(Allyloxy)-N-methyl-2-nitroaniline

The title compound of Example 11 Step A (15.2 mmol, 3.01 g) was stirred in 15 mL of 2 M methylamine in THF at 0°C. After the reaction was complete, the reaction mixture was concentrated under reduced pressure and the residue was partitioned into DCM/brine. The organic phase was concentrated under reduced pressure affording the product as a bright yellow solid. ¹H NMR (500 MHz, d₆-DMSO): δ 8.03 (d, 1H), 6.30 – 6.36 (overlapping m, 2H), 6.06 (m, 1H), 5.44 (m, 1H), 5.31 (m, 1H), 2.96 (d, 3H). MS (ESI): *m/z* 209 (M + H). HPLC A: 2.20 min.

Step C. 5-(Allyloxy)-N-methyl-2-aminoaniline

To a solution of the title compound in Example 11 Step B (7.2 mmol, 1.50 g) in 14.6 mL of 10:1 DMF/H₂O was added SnCl₂ (anhydrous) (5 mmol, 8.1 g). The reaction mixture was heated at 45°C overnight. DCM, followed by NaHCO₃ (aq) was added slowly to the reaction. The resulting precipitate was removed by filtration over celite. The filter cake was washed with DCM, and the combined organic phase was dried with MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 20% EtOAc/hexanes, then 30 % EtOAc/hexanes, affording the desired product as a brown oil. MS (ESI): *m/z* 179 (M + H). HPLC A: 0.89 min.

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Step D. Methyl 4-{[[6-(allyloxy)-1-methyl-1*H*-benzimidazol-2-yl]](4-*tert*-butylcyclohexyl)amino]methyl}benzoate

To the product of Example 1 Step A (3 mmol, 910 mg) and DIEA (3.6 mmol, 626 μ L) in 12 mL of DCM was added thiophosgene (3 mmol, 229 μ L). After 1 h additional DIEA (3.6 mmol) and the title compound of Example 11 Step C (2.75 mmol, 489 mg) were added. After 1.5 h $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ (3 mmol, 1.27 g) was added (exothermic), and the slurry was allowed to stand overnight. HPLC analysis revealed the cyclization was incomplete, so additional $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ (1.5 mmol, 650 mg) was added to the reaction. After 2 h the solution was poured into NaHCO_3 (aq) containing Na_2S , and the slurry was filtered through celite, and the filter cake was washed with DCM. The organic phase was collected and the aqueous phase was extracted with 2x DCM. The combined organic phase was dried with MgSO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 20 % EtOAc/hexanes, then 30 % EtOAc/hexanes affording the product as a foamy solid. ^1H NMR (500 MHz, d_6 -DMSO): δ 7.82 (d, 2H), 7.44 (d, 2H), 7.23 (d, 1H), 6.94 (d, 1H), 6.69 (dd, 1H), 6.06 (m, 1H), 5.40 (m, 1H), 5.24 (m, 1H), 4.56 (m, 2H), 4.51 (s, 2H), 3.79 (s, 3H), 3.57 (s, 3H), 3.16 (m, 1H), 1.96 (m, 2H), 1.79 (m, 2H), 1.58 (m, 2H), 0.94 – 1.12 (overlapping m, 3H), 0.83 (s, 9H). MS (ESI): m/z 490 (M + H). HPLC A: 2.58 min.

Step E. 4-{[[6-(Allyloxy)-1-methyl-1*H*-benzimidazol-2-yl]](4-*tert*-butylcyclohexyl)amino]methyl}benzoic acid

To the title compound of Example 11 Step D (0.1 mmol, 51 mg) in 800 μ L of dioxane was added a solution of LiOH (0.4 mmol, 10 mg) in 400 μ L of H_2O . The resulting solution was stirred at ambient temperature overnight. The reaction mixture was taken up in a pH 7 buffer solution and EtOAc. The mixture was acidified with 2 N HCl until two clear layers formed after agitation. The organic layer was collected and the aqueous layer was washed with EtOAc. The combined organic layers were dried with MgSO_4 and concentrated under reduced pressure to afford the acid as a white solid. MS (ESI): m/z 476 (M + H). HPLC A: 2.33 min.

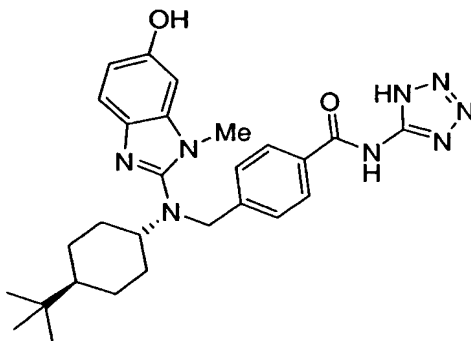
Step F. 4-{[[6-(Allyloxy)-1-methyl-1*H*-benzimidazol-2-yl]](4-*tert*-butylcyclohexyl)-amino]methyl}-*N*-(1*H*-tetraazol-5-yl)benzamide

To a solution of the title compound of Example 11 Step E (0.04 mmol, 20 mg), 1*H*-tetraazol-5-amine monohydrate (0.12 mmol, 12 mg), HOBt (0.08 mmol, 12 mg) and EDC (0.08 mmol, 15 mg) in 1 mL of DMF was added DIEA (0.08 mmol, 14 μ L). The reaction was heated at 40°C for 2 h, then concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/ H_2O and acidified with TFA, then purified by reverse-phase chromatography (Condition B). The product was lyophilized, affording the title compound as a white solid. ^1H NMR (500 MHz, d_6 -DMSO): δ 12.33 (br s, 1H), 8.01 (d, 2H), 7.52 (d, 2H), 7.35 (d, 1H), 7.23 (br unres. m, 1H), 6.91 (br unres. m, 1H), 6.06 (m,

1H), 5.41 (dd, 1H), 5.27 (dd, 1H), 4.75 (s, 2H), 4.62 (d, 2H), 3.73 (s, 3H), 2.01 (m, 2H), 1.82 (m, 2H), 1.69 (m, 2H), 1.16 (m, 2H), 1.03 (m, 1H), 0.85 (s, 9H). one proton obscured by water. MS (ESI): m/z 543 (M + H). HPLC A: 2.19 min.

5

EXAMPLE 12



Step A. Methyl 4-[[[(4-tert-butylcyclohexyl)(6-hydroxy-1-methyl-1H-benzimidazol-2-yl)amino]methyl]benzoate

To a solution of the title compound of Example 11 Step D (0.6 mmol, 300 mg) and 1,3-dimethylbarbituric acid (0.72 mmol, 112 mg) in 3 mL of DCM was added under N₂ a solution of Pd₂dba₃ (0.025 mmol, 23 mg) and 1,4-bis(diphenylphosphino)-butane (0.05 mmol, 21 mg) in 0.5 mL of dry THF which had been incubated under N₂ for 15 min. After 30 min the reaction mixture was concentrated under reduced pressure, then purified by flash chromatography on silica eluting with a step gradient of 1% MeOH/DCM to 4 % MeOH/DCM, affording the product as a white solid. MS (ESI): m/z 450 (M + H). HPLC A: 2.26 min.

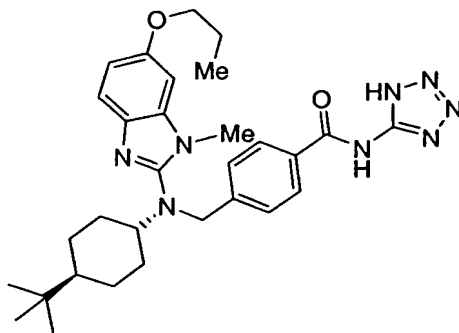
Step B. 4-[[[(4-tert-Butylcyclohexyl)(6-hydroxy-1-methyl-1H-benzimidazol-2-yl)amino]-methyl]benzoic acid

To the title compound of Example 12 Step A (0.1 mmol, 50 mg) in 800 µL of dioxane was added LiOH (0.4 mmol, 10 mg) in 400 µL of H₂O. The resulting solution was stirred at 40°C overnight. The reaction mixture was taken up in aqueous pH 7 buffer and EtOAc, and acidified with 2 N HCl until two clear layers formed after agitation. The organic layer was collected and the aqueous layer was washed with EtOAc. The combined organic layers were dried with MgSO₄ and concentrated under reduced pressure to afford the acid as a white solid, which was used without further purification. (HPLC A: 1.97 min).

Step C. 4-[[[(4-tert-Butylcyclohexyl)(6-hydroxy-1-methyl-1H-benzimidazol-2-yl)amino]-methyl]-N-(1H-tetraazol-5-yl)benzamide

To the product of Example 12 Step B (0.04 mmol), 1*H*-tetraazol-5-amine monohydrate (0.12 mmol, 12 mg), HOBt (0.08 mmol, 12 mg) and EDC (0.08 mmol, 15 mg) in 1 mL of DMF was added DIEA (0.08 mmol, 14 μ L). The reaction was heated at 40°C for 2.5 h, then concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/ H₂O and acidified with TFA, then purified by reverse-phase chromatography (Condition B). The product was lyophilized directly, affording the title compound as a white solid. ¹H NMR (500 MHz, d₆-DMSO): δ 12.35 (br s, 1H), 9.81 (br s, 1H), 8.01 (d, 2H), 7.52 (d, 2H), 7.28 (d, 2H), 6.91 (unres. d, 1H), 6.79 (dd, 1H), 4.75 (s, 2H), 3.69 (s, 3H), 2.01 (m, 2H), 1.83 (m, 2H), 1.69 (m, 2H), 1.16 (m, 2H), 1.04 (m, 1H), 0.85 (s, 9H). One proton obscured by H₂O. MS (ESI): *m/z* 503 (M + H). HPLC A: 1.85 min.

EXAMPLE 13



Step A. Methyl 4-[[[(4-*tert*-butylcyclohexyl)(1-methyl-6-propoxy-1*H*-benzimidazol-2-yl)amino]methyl]benzoate

To a solution of the title compound of Example 12 Step A (0.1 mmol, 45 mg), *n*-propanol (0.25 mmol, 19 μ L) and diisopropyl azodicarboxylate (0.2 mmol, 37 μ L) in 1 mL of DCM was added solid Ph₃P (exothermic). After 20 min the reaction was complete. The product was isolated by flash chromatography on silica eluting with 10% EtOAc/hexanes, then 25% EtOAc/hexanes, affording the product as a clear oil. MS (ESI): *m/z* 492 (M + H). HPLC A: 2.68 min.

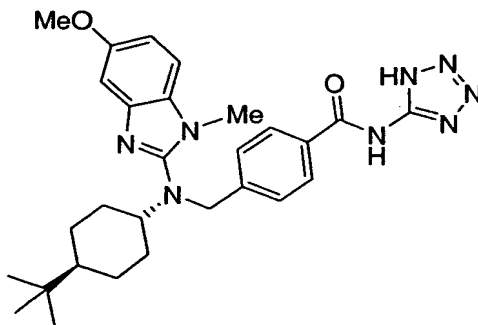
Step B. 4-[[[(4-*tert*-Butylcyclohexyl)(1-methyl-6-propoxy-1*H*-benzimidazol-2-yl)amino]methyl]benzoate

To the title compound of Example 13 Step A (0.07 mmol, 36 mg) in 0.8 mL of dioxane was added LiOH (0.3 mmol, 7 mg) in 0.4 mL of H₂O. The resulting solution was stirred at ambient temperature for 5 h. The reaction mixture was taken up in aqueous pH 7 buffer and EtOAc, and acidified with 2 N HCl until two clear layers formed after agitation. The organic layer was collected and the aqueous layer was washed 2x with EtOAc. The combined organic layers were dried with MgSO₄ and concentrated under reduced pressure to afford the acid as a white solid, which was used without further purification. (HPLC A: 2.42 min).

Step C. 4-[[[(4-*tert*-Butylcyclohexyl)(1-methyl-6-propyloxy-1*H*-benzimidazol-2-yl)-amino]methyl]-*N*-(1*H*-tetraazol-5-yl)benzamide

To a solution of the title compound of Example 13 Step B (0.02 mmol, 10 mg), 1*H*-tetraazol-5-amine monohydrate (0.06 mmol, 6 mg), HOBT (0.04 mmol, 6 mg) and DIEA (0.06 mmol, 10 μ L) in 1 mL of DMF was added EDC (0.04 mmol, 8 mg). The reaction was allowed to stand at ambient temperature overnight, then concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/ H₂O and acidified with TFA, then purified by reverse-phase chromatography (Condition B). The product was lyophilized affording the title compound as a white solid. ¹H NMR (500 MHz, d₆-DMSO): δ 12.34 (s, 1H), 8.00 (d, 2H), 7.53 (d, 2H), 7.43 (d, 1H), 7.20 (br m, 1H), 6.88 (m, 1H), 4.75 (s, 1H), 3.97 (t, 2H), 3.73 (s, 3H), 3.57 (br m, 1H), 2.01 (m, 2H), 1.82 (m, 2H), 1.62 – 1.78 (overlapping m, 4H), 1.16 (m, 2H), 0.95 – 1.08 (overlapping m, 4H), 0.85 (s, 9H). MS (ESI): *m/z* 545 (M + H). HPLC A: 2.28 min.

EXAMPLE 14



Step A. N-Methyl-4-methoxy-2-nitroaniline.

To 4-methoxy-2-nitroaniline (10 mmol, 1.68 g) in 20 mL of DMF was added NaH (12 mmol, 480 mg of a 60 % dispersion in mineral oil) (exothermic, H₂ evolution), affording a deep red slurry. After 15 min MeI (20 mmol, 1.2 mL) was added (exothermic). After 30 min the reaction was poured into a solution of brine and NaHCO₃, resulting in formation of a bright orange precipitate. The slurry was filtered and the filter cake was washed with H₂O. The solid was dried under reduced pressure, affording a bright orange solid. HPLC A: 1.77 min.

Step B. N-Methyl-4-methoxy-1,2-phenylenediamine.

The title compound of Example 14 Step A (3 mmol, 547 mg) and 10 % Pd-C (ca. 50 mg) were stirred in 10 mL of MeOH under H₂ (balloon). After 3 h the solution was nearly colorless. The reaction mixture was filtered over celite and filter cake was washed with MeOH. The combined filtrate was concentrated under reduced pressure affording a slightly orange solid. HPLC A: 0.44 min.

Step C. Methyl 4-[[[4-*tert*-butylcyclohexyl](5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]benzoate

To a solution of the title compound of Example 1 Step B (2.5 mmol, 759 mg) and DIEA (3 mmol, 0.52 mL) in 10 mL of DCM was added thiophosgene (2.5 mmol, 0.19 mL) (exothermic). After 15 min the title compound of Example 14 Step B (3 mmol, 456 mg) and DIEA (3 mmol, 0.52 mL) were added to the solution. After 30 min $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ (2.5 mmol, 1.1 g) was added (exothermic), resulting in formation of an orange precipitate. After 30 min the solution was poured into NaHCO_3 (aq) containing Na_2S , and the slurry was filtered through celite, and the filter cake was washed with DCM. The organic phase was collected and the aqueous phase was extracted with 2x DCM. The combined organic phase was dried with Na_2SO_4 and concentrated under reduced pressure affording a tan solid. Purification by flash chromatography on silica eluting with 25 % EtOAc/hexanes afforded the product as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 7.92 (d, 2H), 7.45 (d, 2H), 7.20 (d, 1H), 7.08 (d, 1H), 6.84 (dd, 1H), 4.63 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.18 (m, 1H), 2.11 (m, 2H), 1.90 (m, 2H), 1.60 (m, 2H), 0.96 – 1.15 (overlapping m, 3H), 0.87 (s, 9H). MS (ESI): m/z 464 (M + H). HPLC A: 2.45 min.

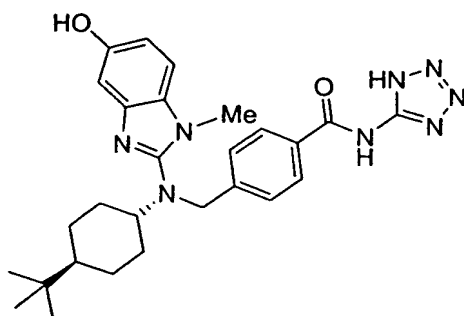
Step D. 4-[[[4-*tert*-Butylcyclohexyl](5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]benzoic acid

To a solution of the title compound of Example 14 Step C (0.2 mmol, 93 mg) in 2 mL of dioxane was added LiOH (2 mmol, 48 mg) in 1 mL of H_2O . The reaction mixture was stirred at 40°C for 1 h. The reaction mixture was taken up in dilute pH 7 buffer and EtOAc, and acidified with 2 N HCl until two clear layers formed after agitation. The organic layer was collected and the aqueous layer was washed 2x with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to afford the acid as a white solid. HPLC A: 2.17 min.

Step E. 4-[[[4-*tert*-Butylcyclohexyl](5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)-amino]methyl]-*N*-(1*H*-tetraazol-5-yl)benzamide

To a solution of the title compound of Example 14 Step D (0.1 mmol, 45 mg), 1*H*-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), HOBt (0.2 mmol, 31 mg) and DIEA (0.3 mmol, 52 μL) in 1 mL of DMF was added EDC (0.2 mmol, 38 mg). The reaction was heated to 40°C for 3 h, then concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/ H_2O and acidified with TFA, then purified by reverse-phase chromatography (Condition B). The product was lyophilized affording a white solid. ^1H NMR (500 MHz, $\text{d}_6\text{-DMSO}$): δ 12.35 (s, 1H), 8.02 (d, 2H), 7.50-7.56 (overlapping m, 3H), 7.00 (d, 1H), 6.96 (m, 1H), 4.81 (s, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.65 (m, 1H), 2.02 (m, 2H), 1.83 (m, 2H), 1.71 (m, 2H), 1.17 (m, 2H), 1.04 (m, 1H), 0.85 (s, 9H). MS (ESI): m/z 517 (M + H). HPLC A: 2.03 min.

EXAMPLE 15



Step A. Methyl 4-([(4-*tert*-butylcyclohexyl)(5-hydroxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl)benzoate

5 To a stirring solution of the title compound of Example 14 Step C (1 mmol, 464 mg) in 5 mL of DCM at -78°C under N_2 was added dropwise BBr_3 (5 mmol, 5 mL of a 1M solution in DCM). The reaction was allowed to warm to ambient temperature. After 15 min the reaction was poured into stirring NaHCO_3 (gas evolution), and the product was extracted with DCM. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure, affording the product as a white solid. ^1H NMR (500
10 MHz, CDCl_3): δ 7.90 (d, 2H), 7.44 (d, 2H), 7.28 (unres. m, 1H), 7.01 (d, 1H), 6.83 (dd, 1H), 4.64 (s, 2H), 3.89 (s, 3H), 3.58 (s, 3H), 3.20 (m, 1H), 2.10 (m, 2H), 1.89 (m, 2H), 1.59 (m, 2H), 0.98 – 1.14 (overlapping m, 3H), 0.86 (s, 9H). MS (ESI): m/z 450 (M + H). HPLC A: 2.30 min.

15 Step B. 4-([(4-*tert*-Butylcyclohexyl)(5-hydroxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl)benzoic acid

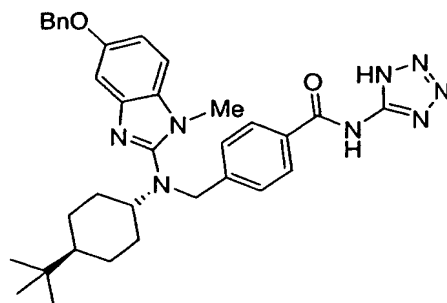
To a solution of the title compound of Example 15 Step A (0.09 mmol, 40 mg) in 1 mL of dioxane was added LiOH (1 mmol, 24 mg) in 0.5 mL of H_2O . The reaction mixture was stirred at 40°C for 1 h. The reaction mixture was taken up in dilute pH 7 buffer and EtOAc, and acidified with 2 N HCl until two clear layers formed after agitation. The organic layer was collected and the aqueous layer
20 was washed 2x with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to afford the acid as a beige solid. HPLC A: 2.01 min.

Step C. 4-([(4-*tert*-Butylcyclohexyl)(5-hydroxy-1-methyl-1*H*-benzimidazol-2-yl)-amino-]methyl)-*N*-(1*H*-tetraazol-5-yl)benzamide

25 To a solution of the title compound of Example 15 Step B (0.02 mmol, 10 mg), 1*H*-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), HOBt (0.2 mmol, 31 mg) and DIEA (0.3 mmol, 52 μL) in 0.5 mL of DMF was added EDC (0.2 mmol, 38 mg). The reaction was heated to 40°C 15 min, then allowed to stand at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/ H_2O and acidified with TFA, then

purified by reverse-phase chromatography (Condition B). The product was lyophilized affording the title compound as a white solid. MS (ESI): m/z 503 ($M + H$). HPLC A: 1.88 min.

EXAMPLE 16



Step A. Methyl 4-[[[(4-*tert*-butylcyclohexyl)(5-benzyloxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]benzoate

To a solution of the title compound of Example 15 Step A (0.2 mmol, 90 mg), benzyl alcohol (0.5 mmol, 52 μ L) and diisopropyl azodicarboxylate (0.4 mmol, 78 μ L) in 1 mL of DCM was added solid Ph_3P (0.4 mmol, 104 mg) (exothermic). After 1 h the product was isolated by flash chromatography on silica eluting with 10% EtOAc/hexanes, then 25% EtOAc/hexanes, affording the product as a waxy solid. HPLC A: 2.76 min.

Step B. 4-[[[(4-*tert*-Butylcyclohexyl)(5-benzyloxy-1-methyl-1*H*-benzimidazol-2-yl)-amino]methyl]benzoic acid

To a solution of the title compound of Example 16 Step A (0.2 mmol, 123 mg) in 2 mL of dioxane was added LiOH (2 mmol, 48 mg) in 1 mL of H_2O . The reaction mixture was stirred at 40°C for 1.5 h. The reaction mixture was taken up in dilute pH 7 buffer and EtOAc, and acidified with 2 N HCl until two clear layers formed after agitation. The organic layer was collected and the aqueous layer was washed 2x with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to afford the acid as a white solid. (HPLC A: 2.49 min).

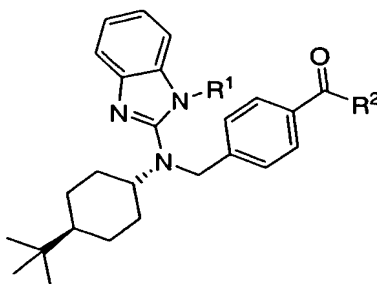
Step C. 4-[[[(4-*tert*-Butylcyclohexyl)(5-benzyloxy-1-methyl-1*H*-benzimidazol-2-yl)-amino]methyl]-*N*-(1*H*-tetraazol-5-yl)benzamide

To a solution of the title compound of Example 16 Step B (0.07 mmol, 37 mg), 1*H*-tetraazol-5-amine monohydrate (0.4 mmol, 41 mg), HOBT (0.4 mmol, 62 mg) and DIEA (0.6 mmol, 104 μ L) in 1 mL of DMF was added EDC (0.4 mmol, 76 mg). The reaction was heated to 40°C for 1 h, then allowed to stand at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/ H_2O and acidified with TFA, then purified by

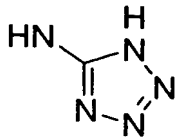
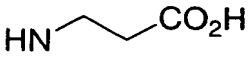
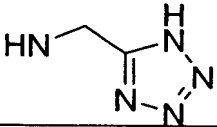
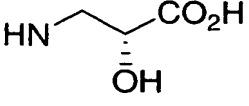
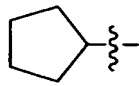
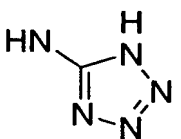
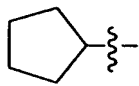
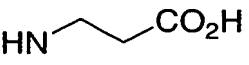
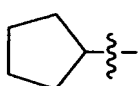
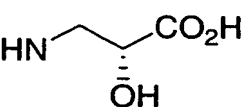
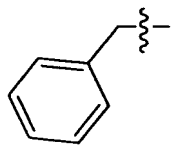
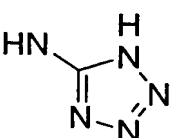
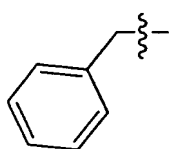
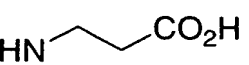
reverse-phase chromatography (Condition B). The product was lyophilized affording the title compound as a white solid. ¹H NMR (500 MHz, d₆-DMSO): δ 12.35 (s, 1H), 8.01 (d, 2H), 7.53 (d, 2H), 7.51 (unres m, 1H), 7.43 (dd, 2H), 7.38 (dd, 2H), 7.32 (tt, 1H), 7.0-7.6 (overlapping m, 2H), 5.16 (s, 2H), 4.79 (s, 2H), 3.73 (s, 3H), 3.63 (m, 1H), 2.01 (m, 2H), 1.82 (m, 2H), 1.69 (m, 2H), 1.16 (m, 2H), 1.03 (m, 1H), 0.85 (s, 9H). MS (ESI): m/z 593 (M + H). HPLC A: 2.38 min.

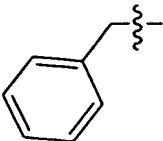
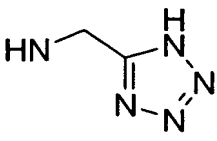
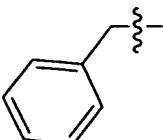
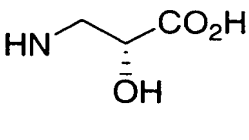
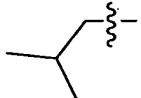
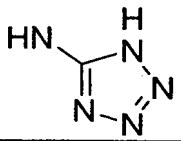
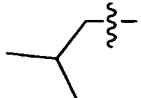
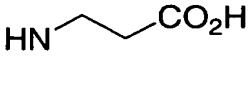
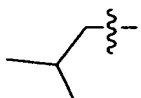
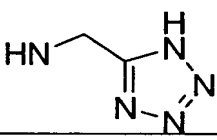
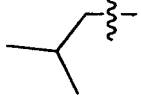
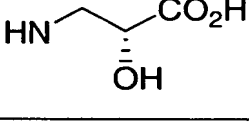
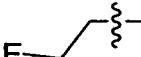
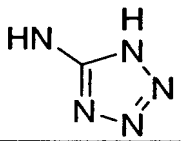
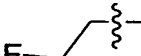
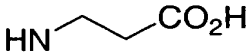
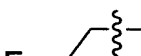
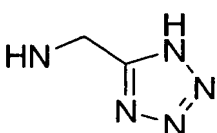
Following the procedures outlined for Examples 1 - 16 the compounds listed in Tables 1 - 9 were prepared

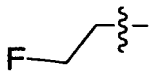
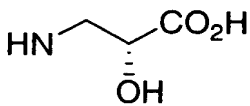
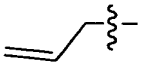
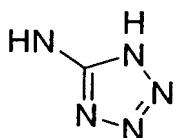
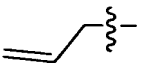
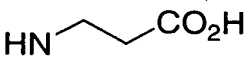
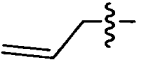
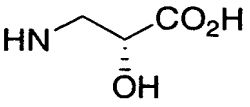
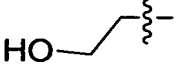
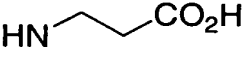
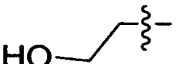
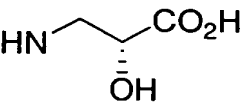
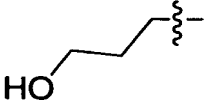
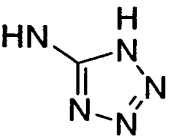
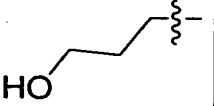
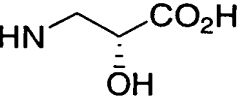
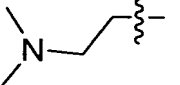
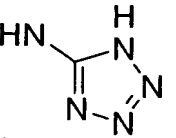
TABLE 1

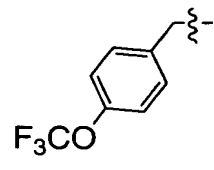
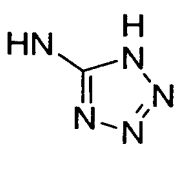
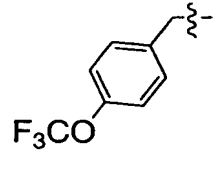
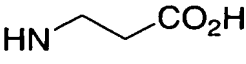
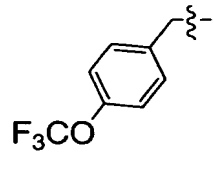
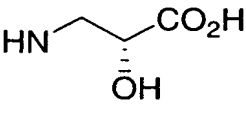
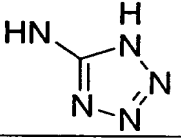
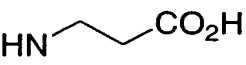
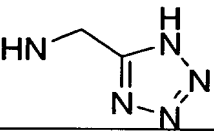
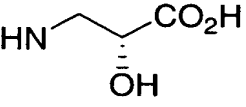
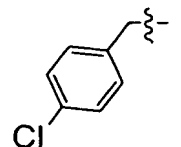
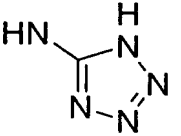


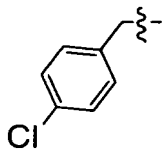
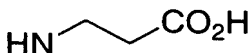
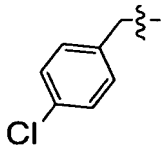
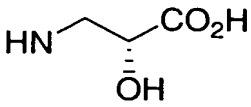
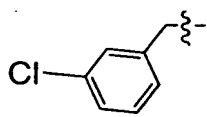
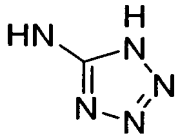
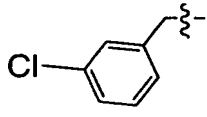
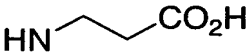
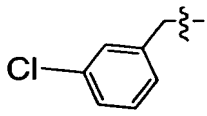
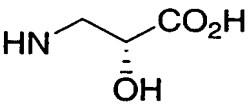
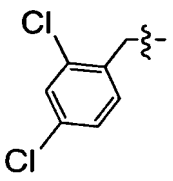
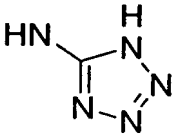
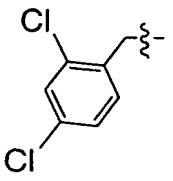
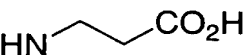
Example	R ¹	R ²	LCMS data: retention time(min) / M + H
17	Et		2.02 / 501.2
18	Et		1.97 / 505.3
19	Et		1.98 / 515.3
20	Et		1.88 / 521.3

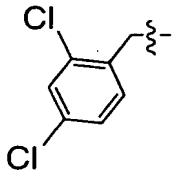
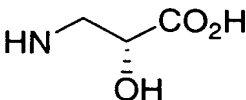
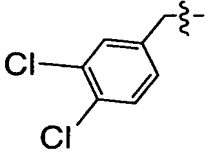
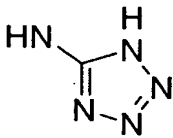
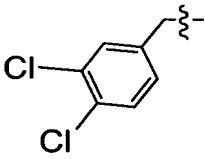
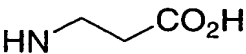
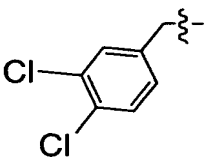
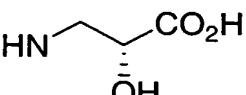
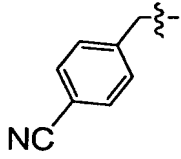
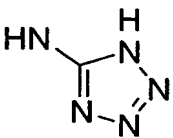
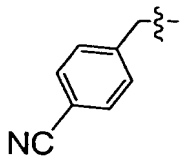
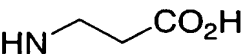
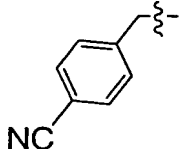
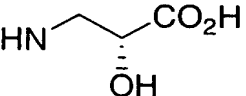
21	Pr		2.15 / 515.3
22	Pr		2.1 / 519.3
23	Pr		2.06 / 529.3
24	Pr		2.01 / 535.3
25			2.30 / 541.3
26			2.24 / 545.3
27			2.16 / 561.3
28			2.34 / 563.3
29			2.28 / 567.3

30			2.27 / 577.3
31			2.2 / 583.3
32			2.25 / 529.3
33			2.19 / 533.4
34			2.18 / 543.3
35			2.11 / 549.3
36			1.99 / 519.3
37			1.94 / 523.3
38			1.92 / 533.3

39			1.86 / 539.3
40			2.13 / 513.4
41			2.08 / 517.4
42			1.99 / 533.4
43			1.75 / 521.3
44			1.68 / 537.3
45			1.84 / 531.4
46			1.70 / 551.5
47			1.54 / 544.5

48			2.59 / 657.4
49			2.53 / 651.4
50			2.46 / 667.4
51	Ph		2.30 / 549.3
52	Ph		2.24 / 553.4
53	Ph		2.223 / 563.4
54	Ph		2.15 / 569.4
55			2.48 / 597.3

56			2.43 / 601.3
57			2.46 / 617.3
58			2.44 / 597.3
59			2.38 / 601.3
60			2.31 / 617.3
61			2.6 / 631.2
62			2.53 / 635.3

63			2.45 / 651.3
64			2.58 / 631.2
65			2.54 / 635.2
66			2.08 / 588.3
67			2.04 / 588.3
68			2.08 / 592.3
69			2.00 / 608.2

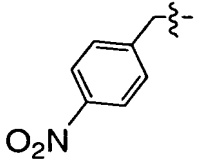
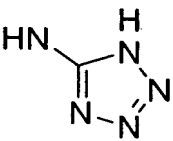
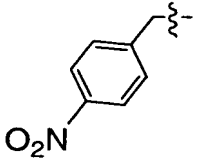
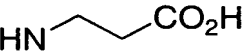
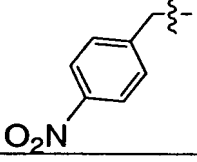
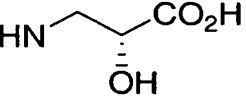
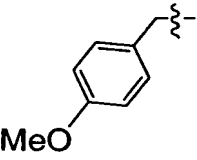
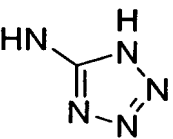
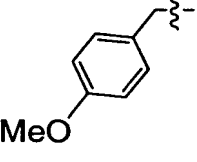

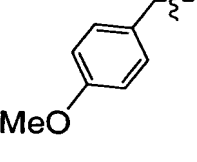
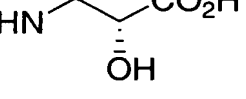
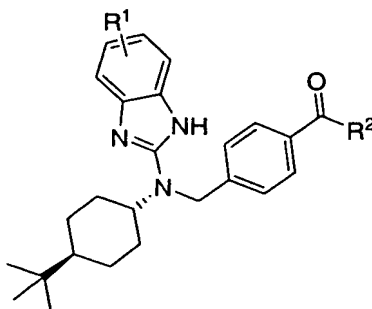
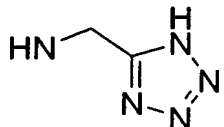
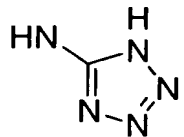
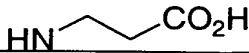
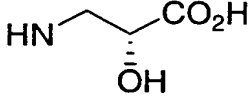
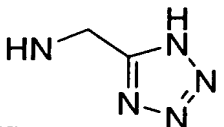
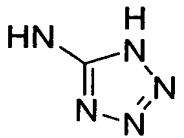
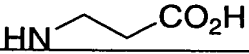
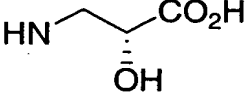
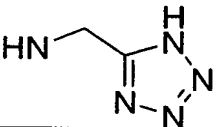
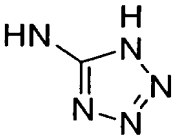
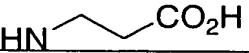
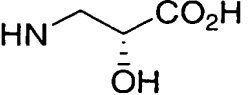
70			2.24 / 608.3
71			2.19 / 612.3
72			2.11 / 628.3
73			2.32 / 593.3
74			2.26 / 597.4
75			2.18 / 613.3

TABLE 2



Example	R ¹	R ²	LCMS data: retention time(min) / M + H
76	5-Me		1.91 / 491.3
77	5-Me		1.96 / 487.3
78	5-CF ₃ O		2.09 / 557.2
79	5-CF ₃ O		2.03 / 561.3
80	5-Cl		1.93 / 507.2
81	5-Cl		1.88 / 511.2
82	5-Me		1.79 / 507.1

83	5-Me		1.87 / 501.3
84	5,6-diCl		2.06 / 541.3
85	5,6-diCl		2.01 / 545.3
86	5,6-diCl		1.92 / 561.3
87	5,6-diCl		2.00 / 555.3
88	5,6-diMe		2.03 / 501
89	5,6-diMe		1.96 / 505
90	5,6-diMe		1.89 / 521
91	5,6-diMe		1.96 / 515
92	5,6-diF		1.93 / 509
93	5,6-diF		1.88 / 513
94	5,6-diF		1.79 / 529

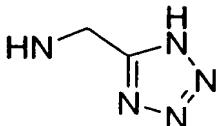
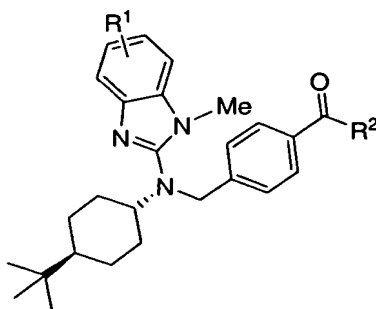
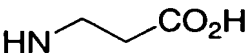
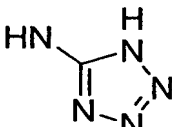
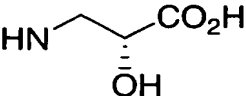
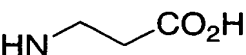
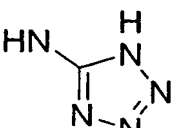
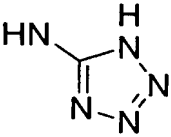
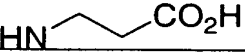
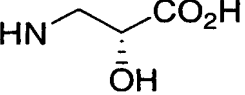
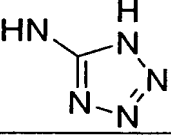
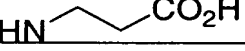
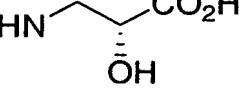
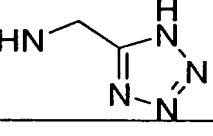
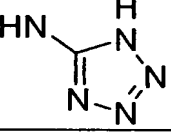
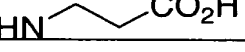
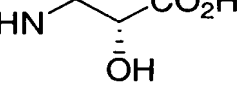
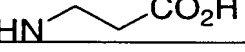
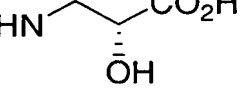
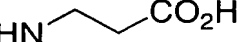
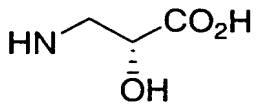
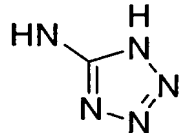
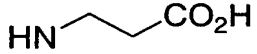
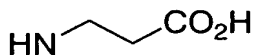
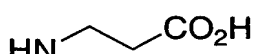
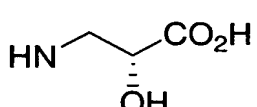
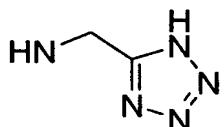
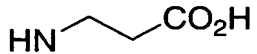
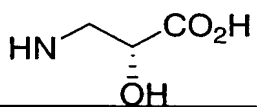
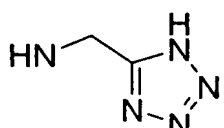
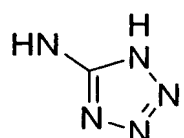
95	5,6-diF		1.87 / 523
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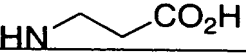
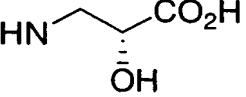
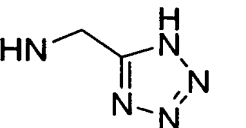
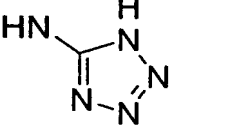
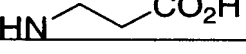
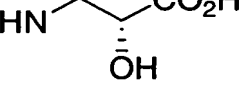
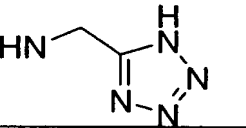
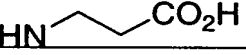
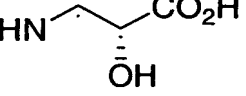
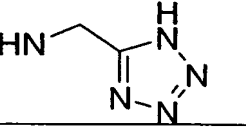
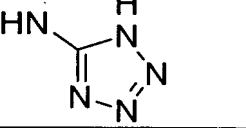

TABLE 3

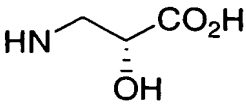
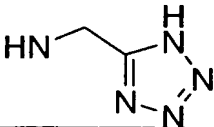
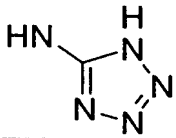
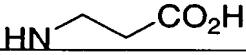
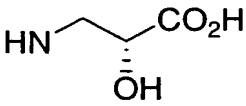
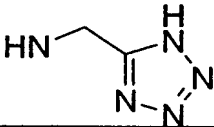
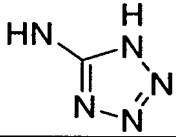
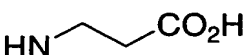
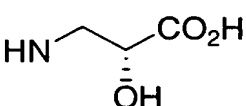
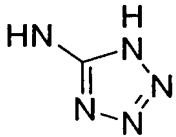
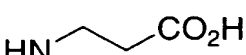
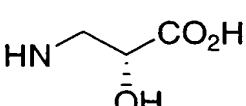


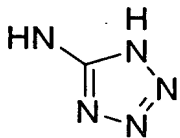
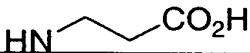
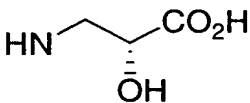
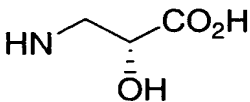
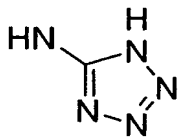
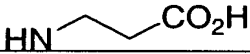
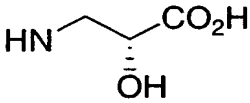
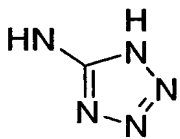
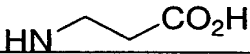
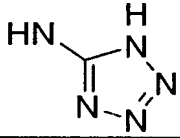
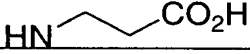
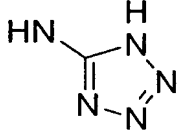
Example	R ¹	R ²	LCMS data: retention time(min) / M + H
96	6-Me		1.99 / 505.3
97	6-Me		2.04 / 501.3
98	6-Me		1.911 / 521.4
99	5-CF ₃		2.13 / 559.3
100	5-CF ₃		2.21 / 555.3

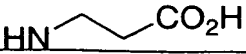
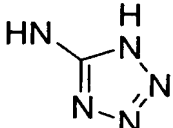
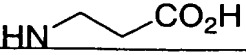
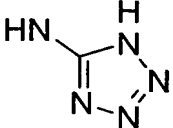
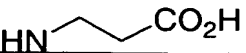
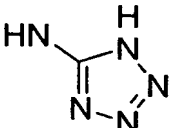
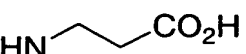
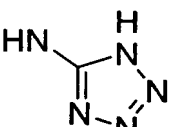
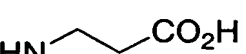
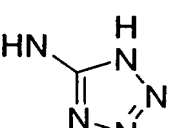
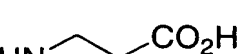
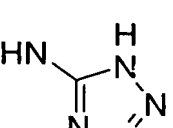

101	5,6-diCl		2.35 / 555.3
102	5,6-diCl		2.24 / 559.3
103	5,6-diCl		2.14 / 575.3
104	5,6-diMe		2.13 / 515
105	5,6-diMe		2.08 / 519
106	5,6-diMe		2.00 / 535
107	5,6-diMe		2.08 / 529
108	5,6-diF		2.08 / 523
109	5,6-diF		2.01 / 527
110	5,6-diF		1.93 / 543
110	5-OMe		1.99 / 521.4
111	5-OMe		1.91 / 537.4
112	5-OH		1.83 / 507.3

113	5-OH		1.74 / 523.3
114	5-OAllyl		2.37 / 593.3
115	5-OAllyl		2.14 / 547.3
116	5-OBn		2.32 / 597.3
117	6-OAllyl		2.14 / 547
118	6-OAllyl		2.07 / 563
119	6-OAllyl		2.14 / 557
120	6-OH		1.8 / 503
121	6-OH		1.72 / 523
122	6-OH		1.79 / 517
123	5-OPr		2.27 / 545.3

124	5-OPr		2.22 / 549.3
125	5-OPr		2.14 / 565.3
126	5-OPr		2.21 / 559.3
127	5-O ⁱ Pr		2.22 / 545.3
128	5-O ⁱ Pr		2.17 / 549.3
129	5-O ⁱ Pr		2.08 / 565.3
130	5-O ⁱ Pr		2.16 / 559.3
131	6-OPr		2.23 / 549
132	6-OPr		2.14 / 565
133	5-OMe		1.97 / 531.3
134	5-O ^c Pentyl		2.4 / 571.3
135	5-O ^c Pentyl		2.36 / 575.3

136	5-O ^c Pentyl		2.28 / 591.4
137	5-O ^c Pentyl		2.34 / 585.3
138	5-O ⁱ Bu		2.40 / 559.3
139	5-O ⁱ Bu		2.35 / 563.4
140	5-O ⁱ Bu		2.28 / 579.4
141	5-O ⁱ Bu		2.34 / 573.3
142	6-OBn		2.38 / 593
143	6-OBn		2.33 / 597
144	6-OBn		2.27 / 613
145	6-O ⁱ Pr		2.22 / 545
146	6-O ⁱ Pr		2.17 / 549
147	6-O ⁱ Pr		2.10 / 565

148	6-OMe		2.02 / 517
149	6-OMe		1.97 / 521
150	6-OMe		1.89 / 537
151	5-OBn		2.27 / 613.4
152	6-O ^c Pentyl		2.42 / 571
153	6-O ^c Pentyl		2.37 / 575
154	6-O ^c Pentyl		2.29 / 591
155	5-OEt		2.14 / 531.3
156	5-OEt		2.008 / 535.4
157	5-O ^c Bu		2.28 / 557.4
158	5-O ^c Bu		2.23 / 561.4
159	5-OCH ₂ ^c Pr		2.24 / 557

160	5-OCH ₂ ^c Pr		2.19 / 561
161	5-OCH ₂ ^c Hex		2.67 / 599
162	5-OCH ₂ ^c Hex		2.62 / 603
163	5-OCH ₂ CHF ₂		2.12 / 567.3
164	5-OCH ₂ CHF ₂		2.08 / 571.3
165	5-OCH ₂ ^c Bu		2.42 / 571
166	5-OCH ₂ ^c Bu		2.38 / 575
167	5-OCH ₂ ^c Pent		2.54 / 585
168	5-OCH ₂ ^c Pent		2.49 / 589
169	6-OEt		2.15 / 531
170	6-OEt		2.10 / 535
171	6-OCH ₂ ^c Pr		2.27 / 557
172	6-OCH ₂ ^c Pr		2.22 / 561

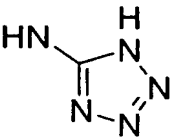
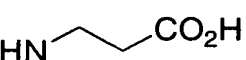
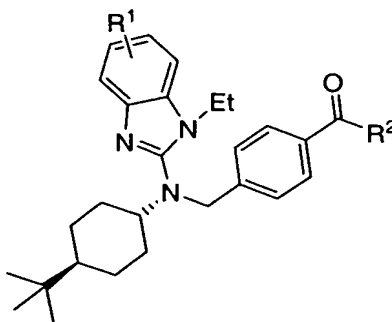
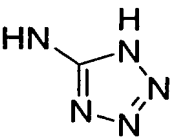
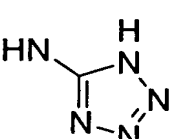
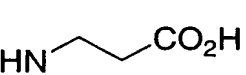
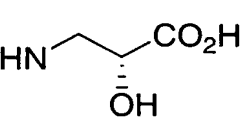
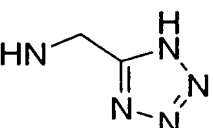
173	6-O ^t Bu		2.42 / 559
174	6-O ^t Bu		2.37 / 563

TABLE 4



Example	R ¹	R ²	LCMS data: retention time (min) / M + H
175	5,6-diCl		2.51 / 569.2
176	6-OAllyl		2.32 / 557
177	6-OAllyl		2.26 / 561
178	6-OAllyl		2.20 / 577
179	6-OAllyl		2.27 / 571

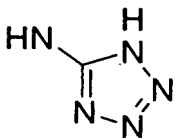
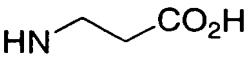
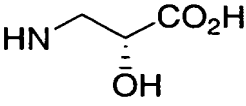
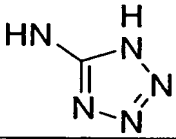
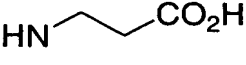
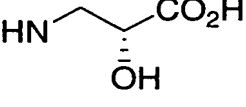
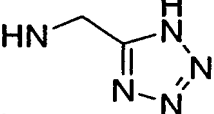
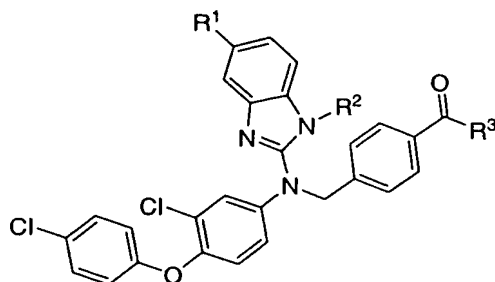
180	5,6-diF		2.24 / 537.3
181	5,6-diF		2.15 / 541.3
182	5,6-diF		2.06 / 577.3
183	6-OH		1.95 / 517
184	6-OH		1.90 / 521
185	6-OH		1.82 / 537
186	6-OH		1.89 / 531

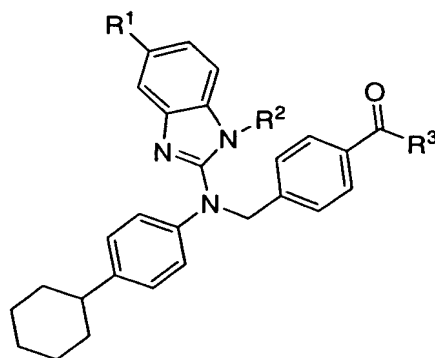
TABLE 5



Example	R ¹	R ²	R ³	LCMS data: retention time(min) / M + H
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187	Me	H	 <chem>NCC(=O)O</chem>	1.97 / 589.1
188	Me	H	 <chem>Nc1nn[nH]1</chem>	2.01 / 585.2
189	CF ₃ O	H	 <chem>NCC(=O)O</chem>	2.11 / 659.1
190	Cl	H	 <chem>Nc1nn[nH]1</chem>	2.01 / 605.0
191	Cl	H	 <chem>NCC(=O)O</chem>	1.96 / 609
192	Me	Me	 <chem>Nc1nn[nH]1</chem>	2.17 / 599.2
193	Me	Me	 <chem>NCC(=O)O</chem>	2.10 / 603.2

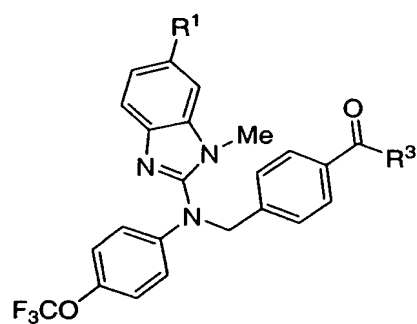
TABLE 6



Example	R ¹	R ²	R ³	LCMS data: retention time(min) / M + H
194	H	H		1.89 / 493.3
195	H	H		1.83 / 497.3
196	H	H		1.74 / 513.3
197	H	Me		2.06 / 507.3
198	H	Me		2.00 / 511.3
199	H	Me		1.91 / 527.3
200	OMe	Me		2.12 / 537.2

201	OMe	Me		2.06 / 541.3
202	OPr	Me		2.35 / 565.2

TABLE 7



Example	R ¹	R ³	LCMS data: retention time(min) / M + H
203	H		1.63 / 509
204	H		1.47 / 529
205	OAllyl		1.91 / 565
206	OAllyl		1.84 / 569
207	OAllyl		1.76 / 585

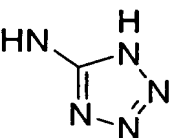
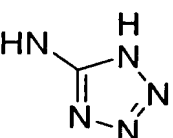
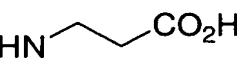
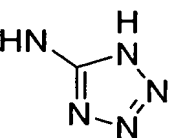
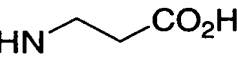
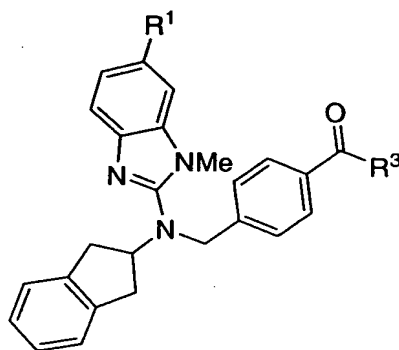
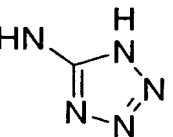
208	OH		1.49 / 525
209	OPr		2.00 / 567
210	OPr		1.94 / 571
211	OBn		2.15 / 615
212	OBn		2.08 / 619

TABLE 8



Example	R ¹	R ³	LCMS data: retention time(min) / M + H
213	H		1.46 / 465.2

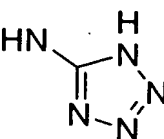
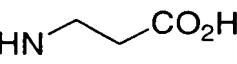
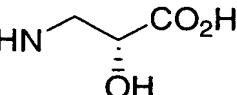
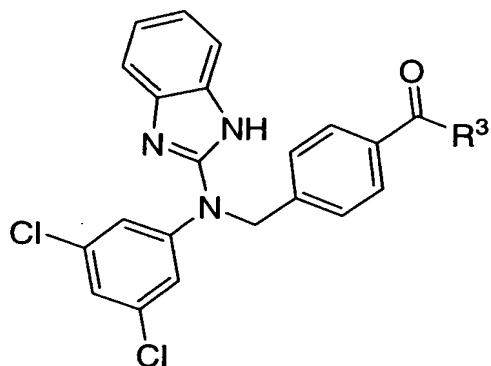
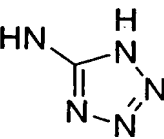
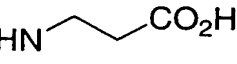
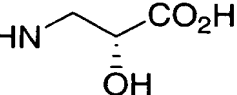
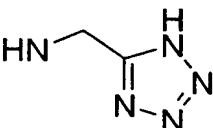
214	OAllyl		1.74 / 521
215	OAllyl		1.68 / 525
216	OAllyl		1.61 / 541

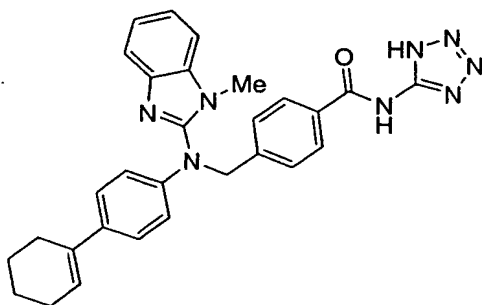
TABLE 9



Example	R ¹	R ³	LCMS data: retention time(min) / M + H
217	H		1.38 / 479
218	H		1.33 / 483
219	H		1.23 / 499

220	H		1.305 / 493
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EXAMPLE 221

Step A. (1E)-1-(4-Bromophenyl)-3-cyclopentyltriaz-1-ene

5 Synthesis of 4-cyclohex-1-en-1-ylphenylamine described below followed the procedure in *J.Org. Chem.*, 1993, 58, 2104.

 To a suspension of 4-bromoaniline (58 mmol, 10 g) in 12 mL of conc. HCl at 0°C was added dropwise an icecold solution of NaNO₂ (58 mmol, 4 g) in 5 mL of H₂O. The resulting mixture was stirred at 0°C for 10 min, then poured into a solution of pyrrolidine (64 mmol, 5.33 mL) in 50 mL of 1 N KOH in an icebath, and the reaction mixture was stirred for 30 min. The resulting brown precipitate was

10 filtered, washed with H₂O, then recrystallized from 50 mL of EtOH, affording the product as a brown crystalline solid.

HPLC A: 2.41 min.

15 Step B. 1-{4-[(1E)-3-Cyclopentyltriaz-1-enyl]phenyl}cyclohexanol

 To a stirring solution of the title compound in Example 221 Step A (3.9 mmol, 1 g) in 30 mL of ether cooled to -78°C was added dropwise *sec*-butyllithium (7.8 mmol, 6.6 mL of a 1.3 M solution in hexanes). The resulting dark red solution was stirred for 30 min at -78°C. Cyclohexanone (7.9 mmol, 820 µL) was added dropwise, and the reaction mixture was allowed to warm to ambient temperature. The

20 reaction was quenched by the addition of 30 mL of H₂O, and the reaction mixture was extracted with 2 x 30 mL of ether. The combined extracts were dried over MgSO₄ and concentrated under reduced pressure, affording a brown oil, which was taken on to Step C without further purification.

Step C. 4-Cyclohex-1-en-1-ylphenylamine

25 The title compound from Example 221 Step B was taken up in a solution of 150 mL of MeOH and 150 mL of 1 N KOH and cooled in an ice bath. To the stirring solution was added in portions

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Al-Ni catalyst (10 g) (gas evolution). The reaction mixture was allowed to warm to ambient temperature and stirred for 5 h, after which time a grey precipitate formed. The slurry was filtered over celite and the filtrate was concentrated under reduced pressure to remove most of the MeOH. The remaining solution was extracted with 2 x 100 mL of ether. The organic phase was concentrated under reduced pressure affording a green oil. The oil was dissolved in 100 mL of benzene, and 50 mg of TsOH, followed by 1 mL of conc. HCl were added to the solution. The resulting reaction mixture was heated to reflux for 30 min, then allowed to cool to ambient temperature. The solution was washed with 100 mL of saturated NaHCO₃, and the organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 10% EtOAc/hexanes, then 15% EtOAc/hexanes, affording the product as a light amber oil. MS (ESI): m/z 174 (M + H). HPLC A: 1.30 min.

Step D. N-(4-Cyclohex-1-en-1-ylphenyl)-1-methyl-1H-benzimidazol-2-amine

To a solution of the title compound from Example 221 Step C (0.59 mmol, 102 mg) and DIEA (0.65 mmol, 113 μ L) in 1 mL of DCM was added thiophosgene (0.62 mmol, 43 μ L). After 30 min, N-methyl-1,2-phenylenediamine (0.9 mmol, 100 μ L) was added and the reaction was stirred overnight at ambient temperature. The reaction mixture was concentrated under reduced pressure and the residue was taken up in 1 mL of DMF. MeI (5.9 mmol, 360 μ L) was added, and the solution was warmed to 50°C for 30 min. The reaction mixture was concentrated under reduced pressure, and crude product was purified by flash chromatography on silica eluting with 0.5:1:98.5 Et₃N/MeOH/DCM, affording the product as a white solid. MS (ESI): m/z 304 (M + H). HPLC A: 1.90 min.

Step E. Methyl 4-{[(4-cyclohex-1-en-1-ylphenyl)(1-methyl-1H-benzimidazol-2-yl)-amino]methyl}benzoate

To the title compound from Example 221 Step D (0.53 mmol, 161 mg) and NaH (0.80 mmol, 32 mg of a 60% dispersion in mineral oil) was added 1 mL of DMF (gas evolution). The mixture was stirred for 30 min at ambient temperature, then methyl 4-(bromomethyl)benzoate (0.80 mmol, 182 mg) was added. After 30 min the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with a step gradient of 10% EtOAc/hexanes, 15% EtOAc/hexanes, and 20% EtOAc/hexanes, affording the product as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.02 (d, 2H), 7.77 (m, 1H), 7.58 (d, 2H), 7.36 (d, 2H), 7.20 – 7.36 (overlapping m, 4H), 6.93 (d, 2H), 6.16 (m, 1H), 5.44 (s, 2H), 3.93 (s, 3H), 3.31 (s, 3H), 2.40 (m, 2H), 2.25 (m, 2H), 1.82 (m, 2H), 1.69 (m, 2H). MS (ESI): m/z 452 (M + H). HPLC A: 2.42 min.

Step F. 4-{[(4-Cyclohex-1-en-1-ylphenyl)(1-methyl-1H-benzimidazol-2-yl)amino]-methyl}benzoic acid

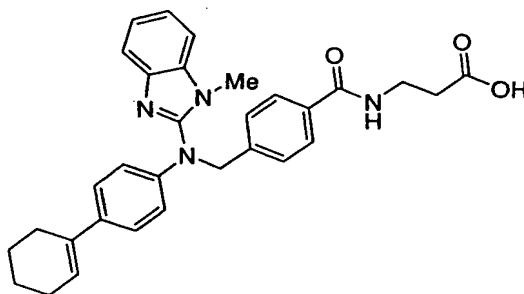
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To the title compound of Example 221 Step E (0.26 mmol, 117 mg) in 2 mL of dioxane was added a solution of LiOH (2.6 mmol, 62 mg) in 1 mL of H₂O. The reaction was stirred at 50°C for 30 min. The dioxane was removed under reduced pressure and the remaining aqueous solution was acidified with 2 N HCl. The resulting precipitate was filtered, washed with H₂O and dried under reduced pressure, affording the product as a white solid. HPLC A: 2.11 min.

Step G. 4-[[[(4-Cyclohex-1-en-1-yl)phenyl](1-methyl-1H-benzimidazol-2-yl)amino]-methyl]-N-(1H-tetraazol-5-yl)benzamide

To a solution of the title compound of Example 221 Step F (0.11 mmol, 50 mg), 1H-tetraazol-5-amine monohydrate (0.23 mmol, 24 mg), HOBt (0.29 mmol, 43 mg) and EDC (0.46 mmol, 88 mg) in 1 mL of DMF was added DIEA (0.57 mmol, 100 µL). The reaction mixture was allowed to stand at ambient temperature overnight, then poured into a mixture of dilute pH 7 buffer/EtOAc, which was acidified with 2 N HCl until two clear layers formed after agitation. The organic phase was concentrated under reduced pressure and the residue was purified by reverse-phase chromatography (Condition B) and lyophilized, affording a white solid. ¹H NMR (500 MHz, DMSO) δ 8.06 (d, 2H), 7.68 (d, 2H), 7.55 (m, 2H), 7.42 (d, 2H), 7.34 (m, 2H), 7.20 (d, 2H), 6.18 (m, 1H), 5.38 (s, 2H), 3.31 (s, 3H), 2.35 (m, 2H), 2.18 (m, 2H), 1.73 (m, 2H), 1.60 (m, 2H). MS (ESI): m/z 505 (M + H). HPLC A: 1.99 min.

EXAMPLE 222



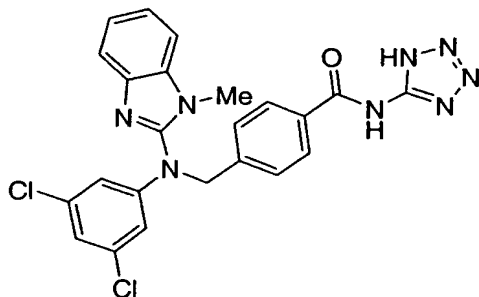
N-(4-[[[(4-Cyclohex-1-en-1-yl)phenyl](1-methyl-1H-benzimidazol-2-yl)amino]methyl]-benzoyl)-β-alanine

To a solution of the title compound of Example 1 Step F (0.01 mmol, 5 mg), the hydrochloride salt of β-alanine tert-butyl ester (0.02 mmol, 4 mg), HOBt (0.03 mmol, 4 mg) and EDC (0.05 mmol, 9 mg) in 0.1 mL of DMF was added DIEA (0.06 mmol, 10 µL). The reaction mixture was allowed to stand at ambient temperature for 4 h, then partitioned between EtOAc/brine. The organic layer was collected and the aqueous phase was extracted twice with EtOAc. The combined organic phase was concentrated under reduced pressure. The residue was treated with 0.5 mL of 2:30:68 H₂O/TFA/DCM for 30 min and the solution was concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (Condition B) and then lyophilized, affording a white solid.

^1H NMR (500 MHz, CD_3OD) δ 7.82 (d, 2H), 7.58-7.43 (m, 8H), 7.32 (d, 2H), 6.21 (m, 1H), 5.38 (s, 2H), 3.61 (2H, t), 3.37 (s, 3H), 2.63 (2H, t), 2.40 (m, 2H), 2.23 (m, 2H), 1.81 (m, 2H), 1.70 (m, 2H). MS (ESI): m/z 509 ($M + H$). HPLC A: 1.92 min.

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EXAMPLE 223

Step A. *N*-(3,5-Dichlorophenyl)-1-methyl-1*H*-benzimidazol-2-amine

To a solution of 3,5-dichloroaniline (6.2 mmol, 1.0 g) and DIEA (6.8 mmol, 1.2 mL) in 10 mL of DCM was slowly added thiophosgene (6.2 mmol, 472 μL) (exothermic). After 30 min, *N*-methyl-1,2-phenylenediamine (6.2 mmol, 704 μL) was added and the reaction mixture was allowed to stand at ambient temperature for 1 h. MeI (6.2 mmol, 386 μL), followed by DIEA (6.8 mmol, 1.2 mL) were then added, and the reaction mixture was allowed to stand at ambient temperature overnight. The crude reaction was partitioned between DCM/brine. The organic layer was collected and the aqueous phase was extracted twice with DCM. The combined organic layer was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 2% MeOH/DCM and 4% MeOH/DCM, affording the product as a tan solid. ^1H NMR (500 MHz, d_6 -DMSO) δ 9.35 (s, 1H), 8.04 (s, 2H), 7.48 (m, 2H), 7.36 (m, 2H), 7.08 – 7.14 (overlapping m, 2H), 3.73 (s, 3H). MS (ESI): m/z 292 ($M + H$). HPLC A: 1.38 min.

20 Step B. Methyl 4-[[[(3,5-dichlorophenyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]-methyl]benzoate

To the title compound from Example 223 Step A (0.21 mmol, 60 mg) and NaH (0.24 mmol, 6 mg of a 60% slurry in mineral oil) was added 0.5 mL of DMF (gas evolution). After 15 min, methyl-4-(bromomethyl)benzoate (0.24 mmol, 55 mg) was added and the reaction mixture was allowed to stand at ambient temperature overnight. The mixture was partitioned between DCM and NaHCO_3 . The organic phase was collected and the aqueous phase was extracted 2 x with DCM. After 30 min the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 2% MeOH/DCM. The product was further purified by reverse phase HPLC (Condition B). The combined HPLC fractions were neutralized with saturated NaHCO_3 and extracted with DCM. The organic phase was dried over MgSO_4 and concentrated under reduced pressure to afford the product as a white solid. ^1H NMR (500 MHz, d_6 -DMSO) δ 7.94 (d, 2H), 7.68 (d, 2H), 7.61

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(d, 1H), 7.52 (d, 1H), 7.21 – 7.29 (overlapping m, 2H), 7.10 (t, 1H), 6.79 (d, 2H), 5.27 (s, 2H), 3.83 (s, 3H), 3.50 (s, 3H). MS (ESI): m/z 440 (M + H). HPLC A: 2.16 min.

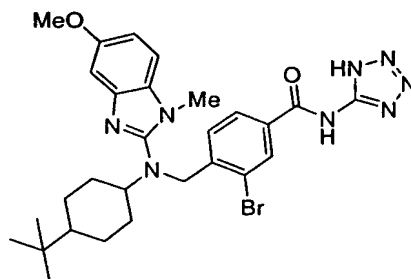
Step C. 4-[[[(3,5-Dichlorophenyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]-benzoic acid

- 5 To the title compound of Example 223 Step B (0.2 mmol, 85 mg) in 1.6 mL of dioxane was added a solution of LiOH (0.8 mmol, 19 mg) in 0.8 mL of H₂O. The reaction was allowed to stir at ambient temperature overnight. The crude reaction mixture was poured into pH 7 buffer/EtOAc, which was acidified with 2 N HCl until two clear layers formed after agitation. The organic phase was collected and the aqueous phase was extracted twice with EtOAc. The combined organic phase was dried over
10 MgSO₄, then concentrated under reduced pressure to afford the product as a white foam. MS (ESI): m/z 426 (M + H). HPLC A: 1.79 min.

Step D. 4-[[[(3,5-Dichlorophenyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]-*N*-(1*H*-tetraazol-5-yl)benzamide

- 15 To a solution of the title compound of Example 223 Step C (0.16 mmol, 68 mg), 1*H*-tetraazol-5-amine monohydrate (0.48 mmol, 49 mg), HOBt (0.32 mmol, 49 mg) and EDC (0.32 mmol, 61 mg) in 1 mL of DMF was added DIEA (0.48 mmol, 83 μ L). The reaction mixture was warmed to 40°C for 2 h, then concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (Condition B). The product was lyophilized, affording a white solid. ¹H NMR (500
20 MHz, d₆-DMSO) δ 12.38 (s, 1H), 8.07 (d, 2H), 7.73 (d, 2H), 7.63 (m, 1H), 7.56 (m, 1H), 7.24 – 7.33 (overlapping m, 2H), 7.15 (t, 1H), 6.90 (d, 2H), 5.31 (s, 2H), 3.53 (s, 3H). MS (ESI): m/z 493 (M + H). HPLC A: 1.69 min.

EXAMPLE 224



25 Step A. Methyl 3-bromo-4-methylbenzoate

- To a solution of 2.0 g (9.3 mmol) of 3-bromo-4-methylbenzoic acid in 25 mL of dichloromethane was added 5.6 mL (11.2 mmol) of oxalyl chloride and 100 μ L of N,N-dimethylformamide. The resultant mixture was stirred at ambient temperature for 2 hours, concentrated in vacuo, and the residue suspended in methanol. The solution was concentrated in vacuo and the residue
30 purified by flash column chromatography (biotage) using 5% ethyl acetate/ hexanes as eluent to provide

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the title compound. ^1H NMR (500 MHz, CDCl_3) δ 8.23 (s, 1H), 7.90 (d, 1H, $J=8$ Hz), 7.33 (d, 1H, $J=8$ Hz), 3.94 (s, 3H), 2.48 (s, 3H). HPLC/MS (ESI) m/z ($M + H$) = 231.0 (3.63 min).

Step B. Methyl 3-bromo-4-bromomethylbenzoate

To a solution of 1.09g (4.76 mmol) of the product from Example 224 Step A in 7 mL of carbon tetrachloride was added 847 mg (4.76 mmol) of N-bromosuccinimide and 78 mg (0.48 mmol) of 2,2'-azobisisobutyronitrile. The resultant mixture was heated at reflux for 25 hours, cooled to ambient temperature, diluted with carbon tetrachloride and filtered through celite. The filtrate was concentrated in vacuo and carried on without purification assuming 100% conversion. HPLC/MS (ESI) m/z ($M + H$) = 310.9 (3.68 min).

Step C. Methyl 3-bromo-4-[(4-*tert*-butylcyclohexyl)amino]methyl]benzoate

To a solution of the product from Example 224 Step B (assume 4.76 mmol) in 5 mL of N,N-dimethylformamide was added 1.02 mL (5.71 mmol) of 4-*tert*-butylcyclohexylamine and 1.7 mL (9.76 mmol) of N,N-diisopropylethylamine. The resultant mixture was stirred at ambient temperature for 3 hours, diluted with ethyl acetate and the organic layer washed sequentially with three portions of water and one portion of saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (biotage) using 5% ethyl acetate/hexanes as eluent to provide both the *cis* isomer and the desired *trans* isomer. ^1H NMR (500 MHz, CD_3OD) δ 8.18 (s, 1H), 7.97 (d, 1H, $J=8$ Hz), 7.58 (d, 1H, $J=8$ Hz), 3.93 (s, 2H), 3.91 (s, 3H), 2.43-2.37 (m, 1H), 2.08-2.01 (m, 2H), 1.85-1.79 (s, 2H), 1.19-0.99 (m, 5H), 0.86 (s, 9H). HPLC/MS (ESI) m/z ($M+H$) = 384.2 (2.47 min.).

Step D. Methyl 3-bromo-4-[(4-*tert*-butylcyclohexyl)(5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]benzoate

To a solution of the title compound from Example 224 Step C (0.5 mmol, 191 mg) and DIEA (0.6 mmol, 104 μL) in 2 mL of DCM was added thiophosgene (0.5 mmol, 38 μL) (exothermic). After 15 min, the title compound from Example 14 Step B (0.6 mmol, 91 mg) was added to the reaction, followed by DIEA (0.6 mmol, 104 μL). The reaction mixture was allowed to stand at ambient temperature for 1 h, then $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ (0.6 mmol, 256 mg) was added (exothermic), affording a pinkish precipitate. After 30 min the solution was poured into saturated NaHCO_3 containing Na_2S , and the slurry was filtered through celite. The filter cake was washed with DCM. The organic layer of the filtrate and washings was collected and the aqueous phase was extracted with 2x DCM. The combined organic phase was dried with Na_2SO_4 and concentrated under reduced pressure affording a brown residue. Purification by flash chromatography on silica eluting with 20% EtOAc/hexanes afforded the product as a slightly green foam. MS (ESI): m/z 542 ($M + H$), 544. HPLC A: 2.67 min.

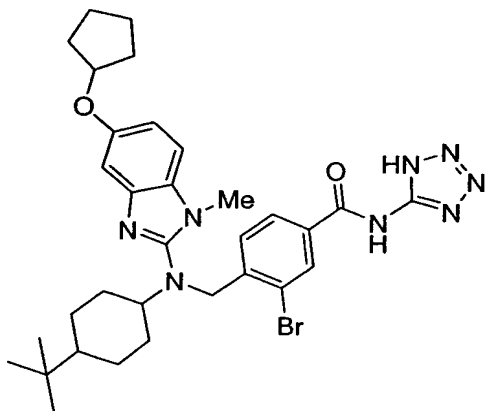
Step E. 3-Bromo-4-[[[(4-*tert*-butylcyclohexyl)(5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]benzoic acid

To the title compound of Example 224 Step D (0.07 mmol, 40 mg) in 2 mL of dioxane was added a solution of LiOH (1 mmol, 24 mg) in 1 mL of H₂O. The reaction was allowed to stir at 40°C for 1.5 h. The crude reaction mixture was poured into pH 7 buffer/EtOAc, which was acidified with 2 N HCl until two clear layers formed after agitation. The organic phase was collected and the aqueous phase was extracted twice with EtOAc. The combined organic phase was dried over Na₂SO₄, then concentrated under reduced pressure to afford the product as a slightly yellow-green foam. HPLC A: 2.32 min.

Step F. 3-Bromo-4-[[[(4-*tert*-butylcyclohexyl)(5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]-*N*-(1*H*-tetraazol-5-yl)benzamide

To a solution of the title compound of Example 223 Step E (0.07 mmol, 40 mg), 1*H*-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), HOBt (0.2 mmol, 31 mg) and EDC (0.2 mmol, 38 mg) in 1 mL of DMF was added DIEA (0.3 mmol, 52 μ L). The reaction mixture was warmed to 40°C for 2 h, then concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (Condition C). The product was lyophilized, affording a white solid. ¹H NMR (500 MHz, d₆-DMSO) δ 12.50 (s, 1H), 8.36 (d, 1H), 7.98 (dd, 2H), 7.60 (d, 2H), 7.51 (dd, 1H), 7.01 (d, 1H), 6.95 (d, 1H), 4.78 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 1.98 (m, 2H), 1.80 (m, 2H), 1.61 (m, 2H), 1.15 (m, 2H), 1.03 (m, 1H), 0.84 (s, 9H). MS (ESI): *m/z* 595 (M + H), 597. HPLC A: 2.17 min.

EXAMPLE 225



Step A. Methyl 3-bromo-4-[[[(4-*tert*-butylcyclohexyl)(5-hydroxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]benzoate

To a stirring solution of the title compound of Example 224 Step D (0.1 mmol, 54 mg) in 1 mL of DCM cooled to -78°C under N₂ was added dropwise BBr₃ (0.3 mmol, 0.3 mL of a 1M solution

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in DCM). The reaction was allowed to warm to ambient temperature. After 1 h the reaction was taken up in 10 mL of MeOH and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 50% EtOAc/hexanes, affording the product as a white solid. HPLC A: 2.54 min.

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Step B. Methyl 3-bromo-4-[[[4-*tert*-butylcyclohexyl](5-cyclopentyloxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]benzoate

To a solution of the title compound of Example 225 Step A (0.08 mmol, 43 mg), cyclopentyl alcohol (0.25 mmol, 23 μ L) and diisopropyl azodicarboxylate (0.25 mmol, 49 μ L) in 0.7 mL of DCM was added Ph_3P (0.25 mmol, 66 mg) (exothermic). After 2 h the product was isolated by flash chromatography on silica eluting with 10% EtOAc/hexanes, then 20% EtOAc/hexanes, affording a waxy yellow solid. HPLC A: 2.97 min.

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Step C. 3-Bromo-4-[[[4-*tert*-butylcyclohexyl](5-cyclopentyloxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]benzoic acid

To the title compound of Example 225 Step B (0.07 mmol, 57 mg) in 2 mL of dioxane was added a solution of LiOH (1 mmol, 24 mg) in 1 mL of H_2O . The reaction was allowed to stir at 40°C for 10 min, then stirred at ambient temperature overnight. The crude reaction mixture was poured into pH 7 buffer/EtOAc, then was acidified with 2 N HCl until two clear layers formed after agitation. The organic phase was collected and the aqueous phase was extracted twice with EtOAc. The combined organic phase was dried over Na_2SO_4 , then concentrated under reduced pressure to afford an oily residue. The residue was triturated in hexanes to afford a beige solid. MS (ESI): m/z 582 ($M + H$), 584. HPLC A: 2.66 min.

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Step D. 3-Bromo-4-[[[4-*tert*-butylcyclohexyl](5-cyclopentyloxy-1-methyl-1*H*-benzimidazol-2-yl)amino]methyl]-*N*-(1*H*-tetraazol-5-yl)benzamide

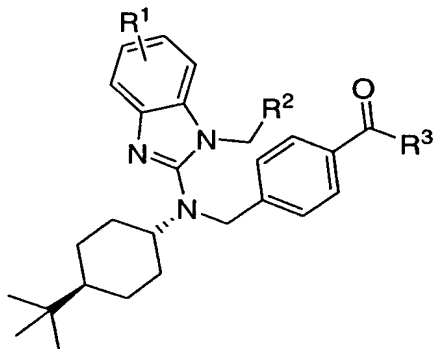
To a solution of the title compound of Example 225 Step C (0.06 mmol, 36 mg), 1*H*-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), HOBt (0.2 mmol, 31 mg) and EDC (0.2 mmol, 38 mg) in 1 mL of DMF was added DIEA (0.3 mmol, 52 μ L). The reaction mixture was warmed to 40°C for 1 h, then concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (Condition D). Lyophilization afforded the product as a white solid. ^1H NMR (500 MHz, d_6 -DMSO) δ 12.49 (s, 1H), 8.35 (d, 2H), 7.97 (dd, 2H), 7.59 (d, 1H), 7.49 (d, 1H), 6.96 (d, 1H), 6.91 (dd, 1H), 4.83 (m, 1H), 4.77 (s, 2H), 3.74 (s, 3H), 3.64 (m, 1H), 1.96 (m, 2H), 1.88 (m, 2H), 1.64 – 1.74 (overlapping m, 4H), 1.52 – 1.64 (overlapping m, 4H), 1.13 (m, 2H), 1.01 (m, 1H), 0.82 (s, 9H). MS (ESI): m/z 649 ($M + H$), 651. HPLC A: 2.51 min.

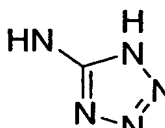
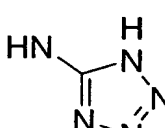
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Following the procedures outlined for Examples 1 - 16 and 221 - 225, the compounds listed in Tables 10 - 12 were prepared

TABLE 10



Example	R ¹	R ²	R ³	LCMS data: retention time(min) / M + H
226	H	Me	HN-CH ₂ -CO ₂ H	2.99 / 491.3
227	H	Me	HN-(CH ₂) ₃ -CO ₂ H	3.00 / 519.3
228	5-Br	H	HN- 	2.12 / 565, 567
229	5-Br	H	HN-CH ₂ -CH ₂ -CO ₂ H	2.05 / 569, 571
230	6-F ₂ CHCH ₂ O	H	HN- 	2.15 / 567.2
231	6-F ₂ CHCH ₂ O	H	HN-CH ₂ -CH ₂ -CO ₂ H	2.10 / 571.3

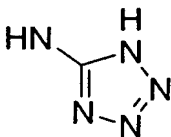
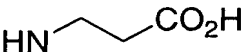
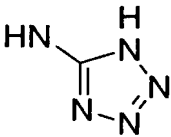
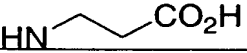
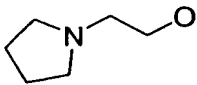
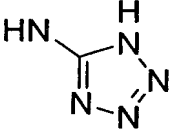
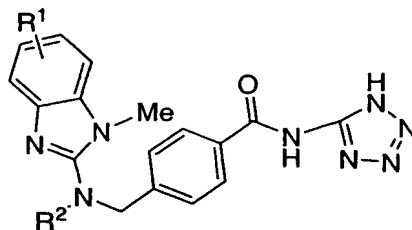
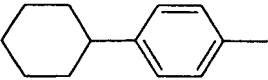
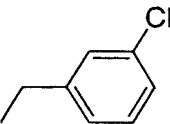
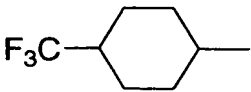

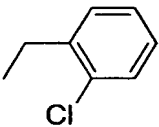
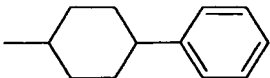
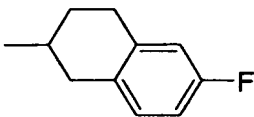
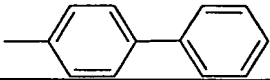
232	6- ^c HexylO	H		2.52 / 585.3
233	6- ^c HexylO	H		2.47 / 589.3
234	6- ^c HexylCH ₂ O	H		2.70 / 599.3
235	6- ^c HexylCH ₂ O	H		2.66 / 603.3
236		H		1.65 / 600.3

TABLE 11



Example	R ¹	R ²	LCMS data: retention time(min) / M + H
237	5-OMe	Ph ₂ CH-	1.67 / 515.2
238	5-O ^c Pent		2.49 / 591.3
239	5-OMe		1.55 / 503.1

240	H		2.65 / 499.2
241	H	4-BrPh	1.48 / 505.1
242	H	4- ^t BuPh	1.81 / 481.2
243	5-MeO	3,5-diClPh	1.72 / 523.1
245	5-OMe		1.58 / 503.1
246	5-OMe		1.50 / 503.1
247	H		2.87 / 507.3
248	H		2.72 / 497.2
249	H		1.75 / 501.3
250	H	4- ⁱ PrPh	1.70 / 467.3
251	H	PhCH ₂ CH ₂	1.39 / 453.2
252	H	PhCH ₂ CH ₂ CH ₂	1.55 / 467.2

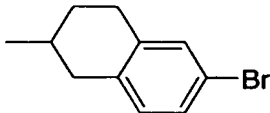
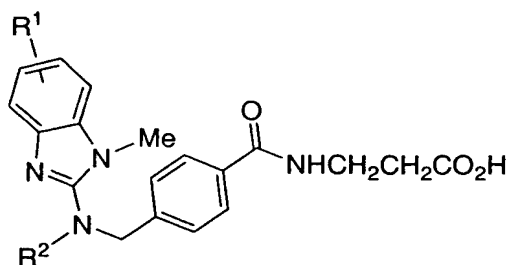
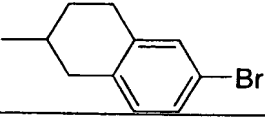
253	H	$\text{PhCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$	1.68 / 481.2
254	H	$4\text{-ClPhCH}_2\text{CH}_2$	1.57 / 487.1
255	5-OPr	3,5-diClPh	2.02 / 551.2
256	5-O ^c Pent	3,5-diClPh	2.17 / 577.2
257	H		2.89 / 559.1
258	5-CF ₃ O	4-CF ₃ OPh	2.22 / 593.1
259	5-CF ₃	4-CF ₃ OPh	2.26 / 577.2
260	5-Cl	4-CF ₃ OPh	1.97 / 543.1
261	5-MeO	4-CF ₃ OPh	1.68 / 539.2
262	5-PrO	4-CF ₃ OPh	1.94 / 567.3
263	5- ^c PentO	4-CF ₃ OPh	2.08 / 593.3

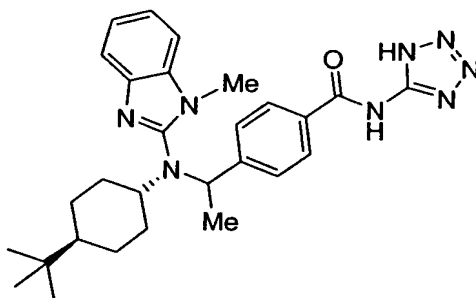
TABLE 12



Example	R^1	R^2	LCMS data: retention time(min) / M + H
264	5-O ⁿ Pent		2.43 / 595.3
265	5-OPr		2.30 / 569.3
266	H		1.66 / 487.3
267	H	4- ^t BuPh	1.75 / 485.2
268	H		2.82 / 511.3
269	H		2.66 / 501.2
270	H		1.70 / 505.3
271	H	4- ⁱ PrPh	1.65 / 471.3

272	H	4-ClPhCH ₂ CH ₂	1.35 / 457.2
273	H		2.89 / 559.1
274	5-MeO	4-CF ₃ OPh	1.62 / 543.2

EXAMPLE 275 / 276

5 Step A. Ethyl 4-{1-[(*trans*-4-*tert*-butylcyclohexyl)amino]ethyl}benzoate

A mixture of ethyl 4-acetylbenzoate (3.00 g, 15.6 mmol), titanium (IV) isopropoxide (9.30 mL, 31.2 mmol), 4-*tert*-butylcyclohexyl amine (4.85 g, 31.2 mmol) in absolute ethanol (100 mL) was stirred under nitrogen at room temperature for 10 h. Sodium borohydride (0.88 g, 23.4 mmol) was then added and the resulting mixture was stirred for an additional 8 h at room temperature. The reaction was quenched by pouring into aqueous ammonia (2N, 225 mL). The resulting inorganic precipitate was filtered off and washed with dichloromethane (100 mL). The organic layer was separated and the remaining aqueous layer was extracted once with dichloromethane (100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. Chromatography (20% EtOAc in Hexane) afforded ethyl 4-{1-[(*trans*-4-*tert*-butylcyclohexyl)amino]ethyl}benzoate. HPLC/MS: *m/z* = 332.3 (M+1), *R*_t = 2.74 min. ¹H NMR (500 MHz, CDCl₃): δ 8.01 (2H, d, *J* = 8.1 Hz), 7.38 (2H, d, *J* = 8.0 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 4.02 (1H, q, *J* = 6.6 Hz), 2.18-2.06 (2H, m), 1.77-1.67 (4H, m), 1.39 (3H, t, *J* = 7.1 Hz), 1.32 (3H, d, *J* = 6.5 Hz), 1.22 (1H, br s), 1.09-0.85 (4 H, m), 0.79 (9H, s).

20 Step B. Ethyl 4-{1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]ethyl}benzoate

To a 0°C solution of ethyl 4-{1-[(*trans*-4-*tert*-butylcyclohexyl)amino]ethyl}benzoate (0.55 g, 1.66 mmol) and DIEA (0.35 mL, 1.99 mmol) in dry dichloromethane (15 mL) was slowly added thiophosgene (0.13 mL, 1.66 mmol). After stirring at 0°C for 10 min and then at room temperature for 45 min, a solution of *N*-methylbenzene-1,2-diamine (0.22 g, 1.83 mmol) and DIEA (0.35 mL, 1.99 mmol) in dry dichloromethane (5 mL) was added. The reaction mixture was stirred for 1 h at ambient temperature and then diluted with dichloromethane (20 mL) and poured into aqueous HCl (1N, 20 mL). The organic layer was separated and washed with aqueous HCl (1N, 20 mL), saturated aqueous NaHCO₃ (20 mL), brine (20 mL), dried over Na₂SO₄ and then concentrated to dryness. The residue was dissolved in dichloromethane (20 mL) and mercury (II) trifluoroacetate (0.80 g, 1.86 mmol) was added. The reaction mixture was stirred for 30 min at room temperature and then filtered through Celite. The organic solution was washed with saturated NaHCO₃ (20 mL), dried over Na₂SO₄ and concentrated. Chromatography (15% EtOAc in Hexane) afforded ethyl 4-{1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]ethyl}benzoate. HPLC/MS: *m/z* = 462.4 (*M*+1), *R*_t = 3.46 min. ¹H NMR (500 MHz, CDCl₃): δ 8.03 (2H, d, *J* = 8.2 Hz), 7.78 (1H, m), 7.52 (2H, d, *J* = 8.2 Hz), 7.28 (3H, m), 4.80 (1H, q, *J* = 6.5 Hz), 4.39 (2H, q, *J* = 7.5 Hz), 3.72 (3H, s), 2.86 (1H, m), 2.14 (1H, m), 1.94 (1H, m), 1.72-1.64 (2H, m), 1.48 (1H, m), 1.41 (3H, t, *J* = 7.5 Hz), 1.17 (3H, d, *J* = 6.5 Hz), 0.95-0.75 (4H, m), 0.73 (9H, s).

Step C. 4-{1-[(*trans*-4-*tert*-Butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]ethyl}-*N*-1*H*-tetrazol-5-ylbenzamide, isomer A and B.

Ethyl 4-{1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]ethyl}benzoate (0.22 g, 0.48 mmol) was dissolved in EtOH/*n*-Heptane (1:1, 9 mL) and eluted with 5% isopropanol in *n*-Heptane on ChiralPak AD column. The fast moving component was collected as isomer A and the slow moving component as isomer B.

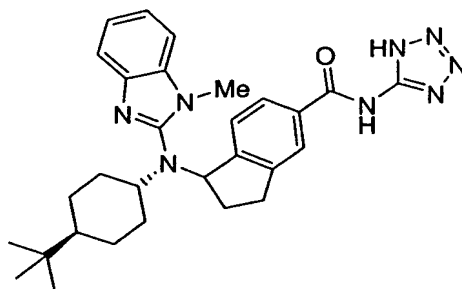
Ethyl 4-{1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]ethyl}benzoate, isomer A (0.10 g, 0.22 mmol) was dissolved in THF/MeOH (1:1, 6 mL) and aq. LiOH (1.0 M, 3 mL) was added. After stirred at room temperature for 16 h, the reaction was neutralized with aqueous HCl (1N, 3.5 mL) until white precipitate started to appear. The resulting mixture was poured into brine (10 mL) and extracted with EtOAc (3x10 mL). The organic extracts were combined, dried over Na₂SO₄ and then concentrated. The residue was dissolved in dry DMF (6 mL) and divided into 3 portions for amide coupling reaction under standard conditions (EDC/HOBt/DIEA in DMF) with 5-amino tetrazole, β-alanine methyl ester and β-hydroxyl β-alanine methyl ester, respectively. For the tetrazole coupling, reaction mixture was loaded directly on HPLC (Xterra C₁₈ column from Waters) and eluted with CH₃CN in H₂O containing 0.1% TFA (20% to 95% over 12 min). Product was freeze-dried from dioxane as a white powder. For coupling reactions with β-alanine methyl ester and β-hydroxyl β-alanine methyl ester, products were purified on silica gel (35% to 45% EtOAc in Hexane).

Methyl ester was subsequently removed with 1.0 M aq. LiOH in THF/MeOH. The resulting carboxylic acids were obtained without further purification.

Isomer A. HPLC/MS: $m/z = 501.4$ ($M+1$), $R_t = 3.01$ min. ^1H NMR ($\text{DMSO}-d_6$): δ 12.40 (1H, s), 8.07 (2H, d, $J = 8.3$ Hz), 7.70-7.67 (2H, m), 7.66 (2H, d, $J = 8.5$ Hz), 7.47-7.42 (2H, m), 4.90 (1H, q, $J = 6.5$ Hz), 3.14 (1H, t, $J = 11.5$ Hz), 2.53 (3H, s), 2.02 (2H, m), 1.68 (2H, m), 1.35 (3H, d, $J = 6.4$ Hz), 1.32-1.24 (1H, m), 1.13-1.06 (1H, m), 0.96-0.78 (3H, m), 0.73 (9H, s).

Isomer B. HPLC/MS: $m/z = 501.4$ ($M+1$), $R_t = 3.02$ min. ^1H NMR ($\text{DMSO}-d_6$): δ 12.40 (1H, s), 8.07 (2H, d, $J = 8.3$ Hz), 7.70-7.67 (2H, m), 7.66 (2H, d, $J = 8.5$ Hz), 7.47-7.42 (2H, m), 4.90 (1H, q, $J = 6.5$ Hz), 3.14 (1H, t, $J = 11.5$ Hz), 2.53 (3H, s), 2.02 (2H, m), 1.68 (2H, m), 1.35 (3H, d, $J = 6.4$ Hz), 1.32-1.24 (1H, m), 1.13-1.06 (1H, m), 0.96-0.78 (3H, m), 0.73 (9H, s).

EXAMPLE 277/278



Step A. (5-Bromo-2,3-dihydro-1H-inden-1-yl)(trans-4-tert-butylcyclohexyl)amine

A mixture of 5-bromoindan-1-one (6.33 g, 30.0 mmol), titanium (IV) isopropoxide (17.8 mL, 60.0 mmol), 4-tert-butylcyclohexyl amine (9.32 g, 60.0 mmol) in absolute ethanol (200 mL) was stirred under nitrogen at room temperature for 12 h. Sodium borohydride (1.70 g, 45.0 mmol) was then added and the resulting mixture was stirred for an additional 8 h at room temperature. The reaction was quenched by pouring into aqueous ammonia (2N, 300 mL). The resulting inorganic precipitate was filtered off and washed with dichloromethane (150 mL). The organic layer was separated and the remaining aqueous layer was extracted once with dichloromethane (150 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated. Chromatography (10% to 20% EtOAc in Hexane) afforded (5-Bromo-2,3-dihydro-1H-inden-1-yl)(trans-4-tert-butylcyclohexyl)amine and the corresponding *cis* product (less polar). HPLC/MS: $m/z = 350.1$ ($M+1$), $R_t = 3.01$ min.

Step B. Methyl 1-[(trans-4-tert-butylcyclohexyl)aminolindane-5-carboxylate

(5-Bromo-2,3-dihydro-1H-inden-1-yl)(trans-4-tert-butylcyclohexyl)amine (1.20 g, 3.42 mmol) was dried azeotropically from dry THF in toluene (3x) and kept under high vacuum for 2 h before use. It was then dissolved in anhydrous THF (20 mL) and cooled to -78°C . n-Butyl lithium (1.6 M solution in Hexane, 8.40 mL, 13.68 mmol) was added over 15 min. After stirring at -78°C for 30 min,

excess dry ice cubes were then added. The reaction mixture was allowed to warm up slowly and then quenched at -20°C with saturated aqueous NH_4Cl (20 mL). Extractions with EtOAc (3x15 mL), drying (Na_2SO_4), filtration and removal of solvent gave the crude carboxylic acid. The crude carboxylic acid was dissolved in MeOH/DCM (1:2, 10 mL) and then (trimethylsilyl)diazomethane (2.0 M solution in Hexane) was added until gas bubbling ceased and the yellow color sustained. Concentration and chromatography (35% EtOAc in Hexane) afforded methyl 1-[(*trans*-4-*tert*-butylcyclohexyl)amino]indane-5-carboxylate. HPLC/MS: $m/z = 330.3$ ($M+1$), $R_t = 2.85$ min.

Step C. Methyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate

To a 0°C solution of methyl 1-[(*trans*-4-*tert*-butylcyclohexyl)amino]indane-5-carboxylate (0.43 g, 1.30 mmol) and DIEA (0.27 mL, 1.56 mmol) in dry dichloromethane (20 mL) was added thiophosgene (0.11 mL, 1.36 mmol) slowly. After stirring at 0°C for 10 min and then at room temperature for 45 min, a solution of *N*-methylbenzene-1,2-diamine (0.38 g, 3.12 mmol) and DIEA (0.53 mL, 3.12 mmol) in dry dichloromethane (5 mL) was added. The reaction mixture was stirred for 1 h at room temperature, then diluted with dichloromethane (30 mL) and poured into aqueous HCl (1N, 30 mL). The organic layer was separated and washed with aqueous HCl (1N, 30 mL), saturated aqueous NaHCO_3 (30 mL), brine (30 mL), dried over Na_2SO_4 and then concentrated to dryness. The residue was dissolved in dichloromethane (30 mL) and mercury (II) trifluoroacetate (0.61 g, 1.43 mmol) was added. The reaction mixture was stirred for 30 min at room temperature and then filtered through Celite. The organic solution was washed once with saturated NaHCO_3 (30 mL), dried over Na_2SO_4 and concentrated. Chromatography (15% EtOAc in Hexane) afforded methyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate. HPLC/MS: $m/z = 460.3$ ($M+1$), $R_t = 3.46$ min. ^1H NMR (CDCl_3): δ 7.85 (1H, s), 7.78 (1H, d, $J = 8.0$ Hz), 7.71 (1H, m), 7.27 (1H, d, $J = 8.5$ Hz), 7.25-7.18 (3H, m), 5.04 (1H, dd, $J = 7.5, 5.0$ Hz), 3.90 (3H, s), 3.48 (3H, s), 3.24 (1H, m), 3.10 (1H, m), 2.83 (1H, m), 2.66 (1H, m), 2.39 (1H, m), 2.21 (1H, m), 1.94 (1H, m), 1.85-1.75 (2H, m), 1.50 (1H, m), 1.36 (1H, m), 1.10-0.94 (2H, m), 0.84 (9H, s).

Step D. 1-[(*trans*-4-*tert*-Butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]-*N*-1*H*-tetrazol-5-ylindane-5-carboxamide.

Methyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate (0.43 g, 0.48 mmol) was dissolved in EtOH/*n*-Heptane (1:1, 9 mL) and eluted with 5% isopropanol in *n*-Heptane on ChiralPak AD column. The fast moving component was collected as isomer A and the slow moving component as isomer B.

Methyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate, isomer A (0.10 g, 0.22 mmol) was dissolved in THF/MeOH (1:1, 6 mL) and aq. LiOH (1.0

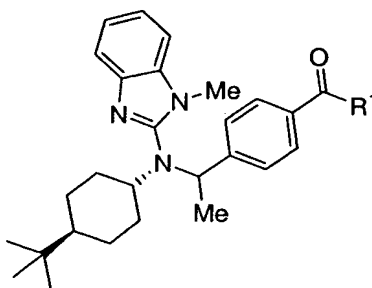
M, 3 mL) was added. After stirred at room temperature for 16 h, the reaction was neutralized with aqueous HCl (1N, 3.5 mL) until white precipitate started to appear. The resulting mixture was poured into brine (10 mL) and extracted with EtOAc (3x10 mL). The organic extracts were combined, dried over Na₂SO₄ and then concentrated. The residue was dissolved in dry DMF (6 mL) and divided into 3 portions for amide coupling reaction under standard conditions (EDC/HOBt/DIEA in DMF) with 5-amino tetrazole, β -alanine methyl ester and β -hydroxyl β -alanine methyl ester, respectively. For the tetrazole coupling, reaction mixture was loaded directly on HPLC (Xterra C₁₈ column from Waters) and eluted with CH₃CN in H₂O containing 0.1% TFA (5% to 70% over 12 min). Product was freeze-dried from dioxane as a white powder. For coupling reactions with β -alanine methyl ester and β -hydroxyl β -alanine methyl ester, products were purified on silica gel (50% to 60% EtOAc in Hexane). Methyl ester was subsequently removed with 1.0 M aq. LiOH in THF/MeOH. The resulting carboxylic acids were obtained without further purification.

Isomer A: HPLC/MS: $m/z = 513.3$ (M+1), $R_t = 3.09$ min. ¹H NMR (DMSO-d₆): δ 10.97 (1H, br s), 7.92 (1H, s), 7.78 (H, d, $J = 7.7$ Hz), 7.60 (1H, d, $J = 8.0$ Hz), 7.48 (1H, d, $J = 8.0$ Hz), 7.42 (1H, d, $J = 8.0$ Hz), 7.40-7.33 (2H, m), 5.35 (1H, t, $J = 7.8$ Hz), 3.72 (3H, s), 3.74-3.52 (2H, m), 3.24-3.18 (1H, m), 3.01-2.94 (1H, m), 2.64-2.58 (2H, m), 2.09 (2H, m), 1.87 (2H, m), 1.68 (2H, m), 1.65 (2H, m), 1.05 (1H, m), 0.87 (9H, s).

Isomer B: HPLC/MS: $m/z = 513.3$ (M+1), $R_t = 3.10$ min. ¹H NMR (DMSO-d₆): δ 10.97 (1H, br s), 7.92 (1H, s), 7.78 (H, d, $J = 7.7$ Hz), 7.60 (1H, d, $J = 8.0$ Hz), 7.48 (1H, d, $J = 8.0$ Hz), 7.42 (1H, d, $J = 8.0$ Hz), 7.40-7.33 (2H, m), 5.35 (1H, t, $J = 7.8$ Hz), 3.72 (3H, s), 3.74-3.52 (2H, m), 3.24-3.18 (1H, m), 3.01-2.94 (1H, m), 2.64-2.58 (2H, m), 2.09 (2H, m), 1.87 (2H, m), 1.68 (2H, m), 1.65 (2H, m), 1.05 (1H, m), 0.87 (9H, s).

Following the procedures outlined above the compounds listed in Tables 13 – 14 were prepared.

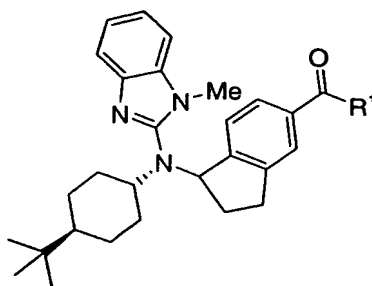
TABLE 13



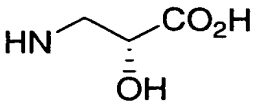
Example	isomer	R ²	LCMS data: retention time(min) / M + H
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279	A		HPLC/MS: m/z = 505.3 (M+1), R _t = 3.06 min.
280	B		HPLC/MS: m/z = 505.3 (M+1), R _t = 3.06 min.
281	A		HPLC/MS: m/z = 521.3 (M+1), R _t = 2.98 min.
282	B		HPLC/MS: m/z = 521.3 (M+1), R _t = 2.98 min.

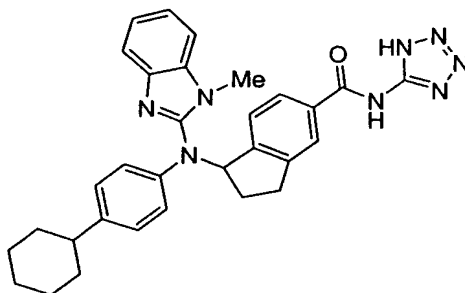
TABLE 14



Example	isomer	R ²	LCMS data: retention time(min) / M + H
283	A		HPLC/MS: m/z = 517.3 (M+1), R _t = 3.04 min
284	B		HPLC/MS: m/z = 517.3 (M+1), R _t = 3.04 min.
285	A		HPLC/MS: m/z = 533.3 (M+1), R _t = 2.93 min.

286	B		HPLC/MS: $m/z = 533.3$ ($M+1$), $R_t = 2.93$ min.
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EXAMPLE 287

Step A. Butyl 1-[(4-cyclohexylphenyl)amino]indane-5-carboxylate

- 5 To a solution of butyl 1-oxoindane-5-carboxylate (2.0 g, 8.60 mmol) and 4-cyclohexylaniline (2.28 g, 20.64 mmol) in 30 mL of anhydrous MeOH was added decaborane $B_{10}H_{14}$ (0.32 g, 2.6 mmol) at room temperature under nitrogen. The resulting solution was stirred at room temperature for 16-48 h. Product butyl 1-[(4-cyclohexylphenyl)amino]indane-5-carboxylate was collected by filtration as a white solid. HPLC/MS: $m/z = 392.3$ ($M+1$), $R_t = 4.97$ min. 1H NMR ($CDCl_3$): δ 7.80 (1H, s), 7.97 (1H, d, $J = 8.0$ Hz), 7.48 (1H, d, $J = 8.0$ Hz), 7.14 (2H, d, $J = 8.5$ Hz), 6.74 (2H, d, $J = 8.5$ Hz), 5.07 (1H, t, $J = 7.1$ Hz), 4.39 (2H, t, $J = 6.7$ Hz), 3.92 (1H, br s), 3.10 (1H, m), 2.97 (1H, m), 2.69 (1H, m), 2.49 (1H, m), 2.02-1.80 (8H, m), 1.60-1.31 (7H, m), 1.08 (3H, t, $J = 7.3$ Hz).

Step B. Butyl 1-[(4-cyclohexylphenyl)(1-methyl-1H-benzimidazol-2-yl)amino]indane-5-carboxylate

- 15 To a $0^\circ C$ solution of butyl 1-[(4-cyclohexylphenyl)amino]indane-5-carboxylate (0.50 g, 1.27 mmol) and DIEA (0.33 mL, 1.90 mmol) in dry dichloromethane (15 mL) was added thiophosgene (0.10 mL, 1.34 mmol) slowly. After stirring at $0^\circ C$ for 10 min and then at room temperature for 1 h, a solution of *N*-methylbenzene-1,2-diamine (0.23 g, 1.90 mmol) and DIEA (0.33 mL, 1.90 mmol) in dry dichloromethane (5 mL) was added. The reaction mixture was stirred for 1 h at room temperature and
- 20 then diluted with dichloromethane (30 mL) and poured into aqueous HCl (1N, 30 mL). The organic layer was separated and washed with aqueous HCl (1N, 30 mL), saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried over Na_2SO_4 and then concentrated to dryness. The residue was dissolved in dichloromethane (30 mL) and excess of mercury (II) trifluoroacetate was added. The reaction mixture was stirred for 30 min at ambient temperature and then filtered through Celite. The organic solution was
- 25 washed with saturated $NaHCO_3$ (30 mL), dried over Na_2SO_4 and concentrated. Chromatography (8% to 15% EtOAc in Hexane) afforded butyl 1-[(4-cyclohexylphenyl)(1-methyl-1H-benzimidazol-2-

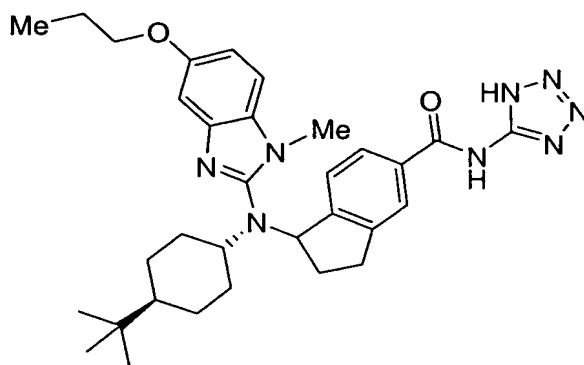
yl)amino]indane-5-carboxylate. HPLC/MS: $m/z = 552.4$ ($M+1$), $R_t = 2.58$ min. ^1H NMR (CDCl_3): δ 7.96 (1H, d, $J = 7.8$ Hz), 7.91 (1H, s), 7.70 (1H, d, $J = 7.5$ Hz), 7.55 (1H, d, $J = 7.5$ Hz), 7.27-7.20 (2H, m), 7.18 (1H, d, $J = 7.5$ Hz), 7.01 (2H, d, $J = 8.5$ Hz), 6.67 (2H, d, $J = 8.5$ Hz), 6.20 (1H, t, $J = 7.5$ Hz), 4.37 (1H, t, $J = 6.5$ Hz), 3.21 (3H, s), 2.91-2.85 (1H, m), 2.77-2.64 (2H, m), 2.46-2.34 (2H, m), 1.86-1.75 (8H, m), 1.54 (2H, m), 1.41-1.24 (6H, m), 1.04 (3H, t, $J = 7.5$ Hz).

Step C. 1-[(4-Cyclohexylphenyl)(1-methyl-1H-benzimidazol-2-yl)amino]-N-1H-tetrazol-5-ylindane-5-carboxamide, isomer B.

Butyl 1-[(4-cyclohexylphenyl)(1-methyl-1H-benzimidazol-2-yl)amino]indane-5-carboxylate (0.10 g, 0.18 mmol) was dissolved in EtOH/n-Heptane (1:1, 4 mL) and eluted with 10% isopropanol in n-Heptane on ChiralPak AD column. The fast moving component was collected as isomer A and the slow moving component as isomer B.

Butyl 1-[(4-cyclohexylphenyl)(1-methyl-1H-benzimidazol-2-yl)amino]indane-5-carboxylate, isomer B (44.0 mg, 0.07 mmol) was dissolved in THF/MeOH (1:1, 6 mL) and aq. LiOH (1.0 M, 3 mL) was added. After stirred at room temperature for 16 h, the reaction was neutralized with aqueous HCl (1N, 3.5 mL) until white precipitate started to appear. The resulting mixture was poured into brine (10 mL) and extracted with EtOAc (3x10 mL). The organic extracts were combined, dried over Na_2SO_4 and then concentrated. The residue was dissolved in dry DMF (2 mL) and coupled with 5-amino tetrazole. Product was purified on HPLC (Xterra C_{18} column from Waters) with CH_3CN in H_2O containing 0.1% TFA (5% to 80% over 12 min) and freeze-dried from dioxane to yield 1-[(4-cyclohexylphenyl)(1-methyl-1H-benzimidazol-2-yl)amino]-N-1H-tetrazol-5-ylindane-5-carboxamide, isomer B. HPLC/MS: $m/z = 533.4$ ($M+1$), $R_t = 2.05$ min. ^1H NMR ($\text{DMSO}-d_6$): δ 12.38 (1H, s), 7.97 (1H, d, $J = 8.0$ Hz), 7.96 (1H, s), 7.77 (1H, d, $J = 7.5$ Hz), 7.56 (1H, dd, $J = 6.0, 3.5$ Hz), 7.51 (1H, m), 7.31 (2H, m), 7.17 (2H, d, $J = 8.5$ Hz), 6.92 (2H, d, $J = 8.0$ Hz), 5.98 (1H, t, $J = 7.5$ Hz), 3.17 (3H, s), 2.91-2.84 (1H, m), 2.72 (1H, m), 2.61 (1H, m), 2.46 (1H, m), 2.33 (1H, m), 1.77-1.18 (11H, m).

EXAMPLE 288



Step A. Butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate

To a 0°C solution of butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)amino]indane-5-carboxylate (0.93 g, 2.5 mmol) and DIEA (0.52 mL, 3.00 mmol) in anhydrous dichloromethane (20 mL) was added thiophosgene (0.20 mL, 2.60 mmol) slowly. After stirring at 0°C for 30 min, a solution of 4-methoxy-*N*¹-methylbenzene-1,2-diamine (0.46 g, 3.00 mmol) and DIEA (0.52 mL, 3.00 mmol) in dry dichloromethane (5 mL) was added. The reaction mixture was stirred for 30 min at room temperature and then diluted with dichloromethane (30 mL) and poured into saturated aqueous NaHCO₃ (30 mL). The organic layer was separated, dried over Na₂SO₄ and then concentrated to dryness. Chromatography afforded 0.94 g (66%) of a mixture of two thiourea intermediates. The mixture of two thioureas was dissolved in dichloromethane (50 mL) and mercury (II) trifluoroacetate (0.78 g, 1.82 mmol) was added. The reaction mixture was stirred for 1 h at room temperature and then filtered through Celite. The filtrate was washed once with saturated NaHCO₃ (30 mL), dried over Na₂SO₄ and concentrated. Chromatography (15% to 20% EtOAc in Hexane) afforded butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate. HPLC/MS: *m/z* = 532.4 (*M*+1), *R*_t = 3.92 min.

Step B. Butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(5-hydroxy-1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate

To a solution of butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(5-methoxy-1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate (0.40 g, 0.75 mmol) in 20 mL of anhydrous dichloromethane at -78 °C was slowly added BBr₃ (1.0 M solution in CH₂Cl₂, 3.8 mL, 3.8 mmol) over 10 min. The reaction mixture was stirred at -78 °C for 30 min and then the cold bath was removed. The reaction was quenched after 20 min with saturated aqueous NaHCO₃ (20 mL) and extracted with EtOAc (3x15 mL). The organic layers were combined, dried over Na₂SO₄ and concentrated. Chromatography afforded butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(5-hydroxy-1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate. HPLC/MS: *m/z* = 518.4 (*M*+1), *R*_t = 2.45 min.

Step C. Butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-5-propoxy-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate

To a solution of butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(5-hydroxy-1-methyl-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate (49.0 mg, 0.095 mmol) in dry dichloromethane was added 1-propanol (18.0 μ L, 0.24 mmol), diisopropyl azodicarboxylate (37.0 μ L, 0.19 mmol) and Ph₃P (50.0 mg, 0.19 mmol). After stirring at room temperature for 2 h, solvent was removed. Chromatography (15% EtOAc in Hexane) afforded butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-5-propoxy-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate. HPLC/MS: *m/z* = 560.5 (*M*+1), *R*_t = 2.43 min.

Step D. 1-[(*trans*-4-*tert*-Butylcyclohexyl)(1-methyl-5-propoxy-1*H*-benzimidazol-2-yl)amino]-*N*-1*H*-tetrazol-5-ylindane-5-carboxamide

Butyl 1-[(*trans*-4-*tert*-butylcyclohexyl)(1-methyl-5-propoxy-1*H*-benzimidazol-2-yl)amino]indane-5-carboxylate (36.0 mg, 0.06 mmol) was dissolved in THF/MeOH (1:1, 6 mL) and aq. LiOH (1.0 M, 3 mL) was added. After stirred at room temperature for 16 h, the reaction was neutralized with aqueous HCl (1N, 3.5 mL) until white precipitate started to appear. The resulting mixture was poured into brine (10 mL) and extracted with EtOAc (3x10 mL). The organic extracts were combined, dried over Na₂SO₄ and then concentrated. The residue was dissolved in dry DMF (2 mL) and coupled with 5-amino tetrazole (EDC/HOBt/DIEA). Product was purified on HPLC (Xterra C₁₈ column from Waters) with CH₃CN in H₂O containing 0.1% TFA (20% to 95% over 12 min) and freeze-dried from dioxane to yield 1-[(*trans*-4-*tert*-Butylcyclohexyl)(1-methyl-5-propoxy-1*H*-benzimidazol-2-yl)amino]-*N*-1*H*-tetrazol-5-ylindane-5-carboxamide. HPLC/MS: *m/z* = 571.5 (*M*+1), *R*_t = 2.16 min. ¹H NMR (DMSO-*d*₆): δ 12.34 (1H, s), 7.98 (1H, s), 7.86 (1H, d, *J* = 8.5 Hz), 7.52 (1H, m), 7.42 (1H, d, *J* = 8.0 Hz), 7.03 (1H, d, *J* = 2.0 Hz), 6.98 (1H, d, *J* = 7.5 Hz), 5.30 (1H, m), 3.67-3.45 (2H, m), 3.95 (2H, t, *J* = 7.0 Hz), 3.71 (3H, s), 3.36 (1H, m), 3.16-3.11 (1H, m), 2.95-2.88 (1H, m), 2.56 (2H, m), 2.00 (2H, m), 1.79-1.70 (4H, m), 1.66-1.51 (2H, m), 1.12-1.05 (2H, m), 0.98 (3H, t, *J* = 7.5 Hz), 0.82 (9H, s).

BIOLOGICAL ASSAYS

The ability of the compounds of the present invention to inhibit the binding of glucagon and their utility in treating or preventing type 2 diabetes mellitus and the related conditions can be demonstrated by the following *in vitro* assays.

Glucagon Receptor Binding Assay

A stable CHO (Chinese hamster ovary) cell line expressing cloned human glucagon receptor was maintained as described (Chicchi et al. *J Biol Chem* **272**, 7765-9(1997); Cascieri et al. *J Biol Chem* **274**, 8694-7(1999)). To determine antagonistic binding affinity of compounds 0.002 mg of cell membranes from these cells were incubated with ¹²⁵I-Glucagon (New England Nuclear, MA) in a buffer containing 50mM Tris-HCl (pH 7.5), 5mM MgCl₂, 2mM EDTA, 12% Glycerol, and 0.200 mg WGA coated PVT SPA beads (Amersham), +/- compounds or 0.001 mM unlabeled glucagon. After 3 hours incubation at room temperature, the radioactivity bound to the cell membranes was determined in a radioactive emission detection counter (Wallac-Microbeta). Data were analyzed using the software program Prism[®] from GraphPad. The IC₅₀ were calculated using non-linear regression analysis assuming single site competition.

Inhibition of Glucagon-stimulated Intracellular cAMP Formation

Exponentially growing CHO cells expressing human glucagon receptor were harvested with the aid of enzyme-free dissociation media (Specialty Media), pelleted at low speed, and re-suspended in the Cell Stimulation Buffer included in the Flash Plate cAMP kit (New England Nuclear, SMP0004A). The adenylate cyclase assay was setup as per manufacturer instructions. Briefly, 5 compounds were diluted from stocks in DMSO and added to cells at a final DMSO concentration of 5%. Cells prepared as above were preincubated in flash plates coated with anti-cAMP antibodies (NEN) in presence of compounds or DMSO controls for 30 minutes, and then stimulated with glucagon (250 pM) for an additional 30 minutes. The cell stimulation was stopped by addition of equal amount of a detection buffer containing lysis buffer as well as ¹²⁵I-labeled cAMP tracer (NEN). After 3 hours of 10 incubation at room temperature the bound radioactivity was determined in a liquid scintillation counter (TopCount-Packard Instruments). Basal activity (100% inhibition) was determined using the DMSO control while 0% inhibition was defined at the amount of pmol cAMP produced by 250pM glucagon.

Certain embodiments of the invention has been described in detail; however, numerous other embodiments are contemplated as falling within the invention. Thus, the claims are not limited to 15 the specific embodiments described herein. All patents, patent applications and publications of any kind that are cited herein are hereby incorporated by reference in their entirety.